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RETENTION IN CARE AND SURVIVAL RATES IN COMORBID CONDITIONS IN PERSONS LIVING WITH HIV

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Dedication

This study is dedicated to my family, professors, friends, and coworkers for their marvelous support and encouragement, as well as to HIV-infected people who struggle with their disease.

This copy does not include the Acknowledgements section

RETENTION IN CARE AND SURVIVAL RATES IN COMORBID CONDITIONS IN PERSONS LIVING WITH HIV

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More than one million people suffer from human immunodeficiency virus (HIV) infections in the United States. Recently, HIV treatments have been developing and improving steadily. Seeing this, persons living with HIV (PLWH) now live longer, but they can also have more chances to experience comorbid conditions. As a result, this dissertation study has two aims.

Aim 1 is a longitudinal retrospective cross-sectional study to investigate the relationships of retention in care measurements, association with symptom burden and retention in care, and association between disease control and retention in care between PLWH with diabetes (DM).

Aim 2 is a longitudinal retrospective comparison study to compare the chronic kidney disease (CKD) occurrences between PLWH and PLWH+DM from 2006 through 2015, and to compare the survival rates differences among PLWH, PLWH+DM, and PLWH+DM with CKD.

In Aim 1, a total of 798 samples who had PLWH+DM in 2015 participated in this study. Most of the retention in care in PLWH+DM measurements were significantly correlated ($p < 0.05$). As to disease control, only CD4 cell count had relationships with retention in care measurements in all age groups, and hemoglobin A1c (HbA1c) level only occurred as a significant relationship with younger adults living with HIV with DM (YALWH+DM). Having the additional burden of some symptoms negatively affects retention in care in older adults living with HIV with DM (OALWH+DM).

In Aim 2, a total of 10,063 samples had HIV infections in study. With having more comorbid conditions as well as increasing age at initial clinic visit, mortality rates increased. The mean survival time was 19.689 years (95% CI: 19.572-19.806). Having DM with PLWH, the mortality rates were three times higher than PLWH-only, and as for patients having DM with CKD in PLWH, the mortality rate was three times higher than PLWH+DM.

According to the study, retention in care in PLWH+DM affects disease control and symptom burden (fatigue, sadness, memory loss) negatively in regard to the retention in care in OALWH+DM. Moreover, comorbid conditions have negative association with length of survival. Based on these findings, this study will contribute to the knowledge of comorbid conditions in PLWH as it applies to nursing practice, research, and policy.

Key words: HIV; PLWH; retention in care; survival rates; symptom burden

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Chapter One: Introduction

This chapter will present the introduction of the study. It contains the study's background; the significance of persons living with human immunodeficiency virus (HIV) (PLWH), PLWH with diabetes (DM), and PLWH with chronic kidney disease (CKD); the conceptual model, major concepts and definitions related to the study; assumptions for the summary; and limitations.

HIV IN AMERICA

Current HIV Trends in the United States of America

PLWH are individuals who are infected with the HIV (AIDS Info, 2016e). The HIV infection causes an impaired immune system (AIDS Info, 2016e) because the virus destroys CD4 cells (T cells), which are white blood cells key in fighting infections (AIDS Info, 2016e). Researchers identified HIV more than 30 years ago in 1983 (AIDS Info, 2016d). More than 1.2 million people live with HIV (CDC, 2017b) and 50,000 patients are newly HIV-infected each year in the United States (CDC, 2016). Moreover, an estimated 12.8% (156,300) are not unaware of their HIV infection (AIDS Info, 2016d).

The U.S. Centers for Disease Control and Prevention (CDC) created a 3 stage classification system based on CD4 cell count levels, which measures immune system function: Stage 1—CD4 cell count greater than or equal to 500 cells/μL; Stage 2—200-499 cells/μL; and Stage 3—less than 200 cells/μL (Castro et al., 1993). Stage 3, or diagnosis of acquired immunodeficiency syndrome (AIDS) leads to other infections caused by the HIV infection (AIDS Info, 2016e). If it is not treated for appropriately, HIV infections can progress to stage 3 (CDC, 2016), which is at that point called AIDS (Castro et al., 1993). The survival rate for someone diagnosed with stage 3, or AIDS is only three years (AIDS Info, 2016e) and cannot reverse damage to immune systems. The CDC estimated that of there are 44,073 people was diagnosed HIV; among them, 20,786 people progressed to AIDS in 2014 (CDC, 2016).

Before development of HIV/AIDS treatments, the CDC in 1981 estimated that almost 658,507 people died due to AIDS (CDC, 2016). In the mid of 1990s, HIV/AIDS treatments developed significantly, particularly combined antiretroviral therapy (cART) (Arts, & Hazuda, 2012). The survival rates of PLWH increased significantly in the late 1990s (CDC, 2017a; Oppenheim, 2009), and now, more than 80% can live ten years after seroconversion (Oppenheim, 2009). cART contributes to improved immune function, increases CD4 cell count, and sustains a low viral load (VL) (Autran et al., 1997; Mahy, Autenrieth, Stanecki, & Wynd, 2014; Mpondo, 2016). VL indicates the amount of HIV in a patient's body, and evaluating the amount of VL helps to assess health status and evaluate the effectiveness of cART (AIDS Info, 2015b). The general population does not have VL, but if people have an HIV infection, they have VL in their bodies (AIDS Info, 2015b). VL suppression is important to PLWH because if PLWH sustained VL suppression, they can prevent HIV progression to stage 3 (AIDS) and reduce the HIV transmission (AIDS Info, 2015b), VL suppression is defined of PLWH who already adhere to cART, having at least one an undetectable VL more than three months apart within one year (Nosyk et al., 2014). Having cART thus prevents the progress of HIV (Winston & Underwood, 2015). As a result of the development of cART, we can currently expect the life expectancy of PLWH to reach the early 70s if patients are prescribed the correct medication and adhere to a cART regimen (Samji et al,, 2013).

HIV TREATMENTS

Since 1996, the main treatment for PLWH has been cART (Arts, & Hazuda, 2012). Highly active antiretroviral therapy (HARRT) or cART, therapy drastically reduced HIV-related morbidity and mortality rates (Mahy et al., 2014; Mpondo, 2016) by preventing the progress of HIV disease (Winston & Underwood, 2015). Since cART has been implemented, HIV infection is considered a chronic condition and a manageable disease (Braithwaite et al., 2005; Winston & Underwood, 2015). By 2015, approximately 15 million people achieved life saving after cART (Joint United Nations Programme on HIV/AIDS, 2013).

There is debate on the initiation of treatment. According to the U.S. Department of Health and Human Services (HHS) Guidelines, cARTs are recommended to all PLWH regardless of any CD4 cell count level (HIV/AIDS Bureau, 2014). The other point of view is the WHO guidelines recommend that cART be initiated for CD4 cell count of less than 500 cells per μL in PLWH (World Health Organization, 2015). Both of the guidelines indicated that it is important to receive cART in PLWH. This occurs because having early retention in care is one of the improvements in managing HIV (Geng et al., 2010), which results in positive health outcomes (Horstmann, Brown, Islam, Buck, & Agins, 2010; Mugavero, Amico, et al., 2012; Mugavero, Davila, Nevin, & Giordano, 2010).

There are six drug classifications in cART: non-nucleoside reverse transcriptase inhibitors (NNRTIs; non-nucleoside reverse transcriptase inhibitor); nucleoside reverse transcriptase inhibitors (NRTIs; nucleoside reverse transcriptase inhibitors); protease inhibitors (PIs; block HIV protease); fusion inhibitors (block HIV from entering the CD4 cells), CCR5 antagonist (CCR5s; block proteins on the CD4 cells); and integrase strand transfer inhibitors (INSTIs; block HIV integrase) (AIDS Info, 2015a). The current HHS guidelines recommend using cART mixed more than two different classification medications in PLWH (AIDS Info, 2016c).

HIV DISEASE CONTROL: CD4 CELL COUNT AND VL

HIV control and disease progression is monitored through two laboratory values: CD4 cell count and VL (Ford et al., 2015). First, CD4 cell count is a type of white blood cell that plays a key role in fighting infections (AIDS Info, 2016b). The higher the CD4 cell count, the better one can fight infection (AIDS Info, 2016b). Low CD4 cell count has been associated with disease progression treatments, cART leads to an increase in CD4 cell count or CD4 recovery (Ellis et al., 2011). It is important to monitor a patient's CD4 cell count every four to six months in order to monitor the efficacy of cART (Ford et al., 2015). The general population have a CD4 cell count from 500 cells/μL to 1,600 cells/μL (AIDS Info, 2016b). The target CD4 cell count in PLWH

should increase 50 to 100 cells/μL per year for adequate management, which indicates competent management of HIV infections (AIDS Info, 2016c).

VL is a laboratory value that measures the level HIV virus in a blood sample (AIDS Info, 2015b). Having a high VL means having more HIV infections and it indicates that the immune system is not working well (AIDS Info, 2015b). The medical goal is to have an undetectable VL means the virus is barely detectable by laboratory analysis and decreases the likelihood that the HIV virus will be transmitted (AIDS Info, 2015b). National HIV/AIDS strategy set a goal of 80% of PLWH will have an undetectable VL (White House Office of National AIDS Policy, 2015). PLWH who have low VL, are referred to PLWH as, having VL suppression, but it does not mean that HIV is cured (AIDS Info, 2016a). PLWH can achieve VL suppression by taking HIV medications (cART) every day and exactly as prescribed (AIDS Info, 2016a).

BACKGROUND AND SIGNIFICANCE

This study is significant because if focuses on (1) health outcomes of the growing segment of PLWH, the older adults (OA) with HIV, (2) comorbid conditions in PLWH, and (3) the HIV treatment cascade.

Focus on OALWH

According to previous studies, OA living with HIV (OALWH) are considered to be those over 50 years old, which which is often called older age (Emlet, 2006; Legarth et al., 2016; Savasta, 2004; Webel et al., 2014). In the general public, OA is usually set five years later at 55 in previous studies (Omvik, Pallesen, Havik, Kvale, & Nordhus, 2006; Petry, 2002), however for PLWH the younger threshold is due to premature aging caused by chronic inflammation and activated immune response (Nasi et al., 2016). Due to this prolonged life expectancy, the population of OA with HIV is growing notably (Effros et al., 2008) compare with the pre-cART. The prevalence of OALWH increased steadily, from 19% to 25%, between 2001 and 2007 (Operskalski, Mosley, Busch, & Stram, 1997), and they make up 17% of PLWH in 2014 (CDC, 2017c).

OALWH have different characteristics than younger adults living with HIV (YAPLWH). In particular, a lack of adequate social supports (living alone, health insurance status) and age-related comorbid conditions exist (Emlet & Farkas, 2002). Only 23.3% of YALWH lived alone, while 36.0% of OALWH lived alone (Emlet & Farkas, 2002). Approximately 42.3% of OALWH had private insurance compared with only 35.6% of YALWH (Emlet & Farkas, 2002). Nearly 30% of OALWH had more than two chronic conditions (Negin et al., 2012).

Almost forty-two percent of OALWH in the United States died in 2013 (CDC, 2014a). Mortality in OALWH is related to age-related comorbid health conditions rather than being directly attributable to HIV infection (Braithwaite et al., 2005). This indicates that taking care of OALWH with comorbid conditions is important to positive health outcomes. For these reasons, age-related research studies for HIV-infected OA in the essential area of management of comorbid conditions are needed (Braithwaite et al., 2005; Martin, Fain, & Klotz, 2008). We thus need more studies on comorbid conditions in OALWH to prevent HIV progression and ultimately reduce HIV-related mortalities.

Comorbid Conditions in PLWH: DM and CKD

Due to compromised immune systems (Wooten-Bielski, 1999) and side effects of cART (Brown, et al., 2010; Kalra & Agrawal, 2013; Spollett, 2006), PLWH will have increased chance of developing age-related chronic diseases than people who do not have HIV (Mpondo, 2016; Negin et al., 2012; Vigouroux et al., 1999; Webel et al., 2015). Two of the most often diagnosed chronic conditions are DM and CKD (Brown et al., 2005; Adeel A Butt et al., 2009; Medapalli et al., 2012; Naicker, Rahmania, & Kopp, 2015).

PLWH+DM

Among PLWH, DM is the second-most common comorbid condition, and approximately 15% of PLWH have DM (Brown et al., 2005; Butt et al., 2009; Medapalli et al., 2012). More than 29.1 million people (9.3%) in the U.S. general population have DM (CDC, 2014b). In addition, DM is a leading factor in non-HIV-related deaths (Rolls, Denneny, Marcus, & O'Connell, 2014).

The most likely reason that PLWH have DM is the cARTs' side effect, which is glucose intolerance (Brown et al., 2005; De Wit et al., 2008; Kim et al., 2011; Ledergerber et al., 2007). As a result of the cumulative exposure to cART, one of the cART HIV-1 protease inhibitors (PIs), has an adverse metabolic effect (Dagogo-Jack, 2008). It increases insulin resistance and impairs insulin secretion. Presently, the mechanism of PI-induced insulin resistance is not defined (Schütt, Zhou, Meier, & Klein, 2004), but PI inhibit the cellular glucose transport system (Hruz, Murata, Qiu, & Mueckler, 2002). PIs are also an activator of the insulin receptor tyrosine kinase, which creates insulin resistance (Cheng et al., 2004).

DM Disease Control: HbA1c level

Hemoglobin A1c (HbA1c) level is an indicator of metabolic control in DM (Diop et al., 2006) because it indirectly measures glucose level over the previous three months (Nasir, Thevarajah, & Yean, 2010). The American Diabetes Association (ADA) endorsed the standard that the presence of DM is confirmed when HbA1c level is greater than 6.5% (American Diabetes Association, 2017) but there are no specified HbA1c level goals by age. Previous studies measuring the DM control in PLWH used a HbA1c cutoff level of 6.5% (Eckhardt, Holzman, Kwan, Baghdadi, & Aberg, 2012; Tien et al., 2012). Despite this, the HbA1c level cutoff level in OA without major comorbidities is 7-7.5% in the general population (Kirkman et al., 2012). Thus, we may accept this criterion in PLWH with comorbid conditions. But still, no gold standard criterion exists in PLWH+DM (Tien et al., 2012). For this study, however, the researcher used a HbA1c cutoff level of 6.5% because the CNICS defined DM based by this criteria.

PLWH+CKD

CKD is a common complication of HIV infection and is three times more likely to develop in PLWH than in the general population (Bonjoch et al., 2014; Ibrahim et al., 2012; Islam, Wu, Jansson, & Wilson, 2012; Schwartz et al., 2005). The major reason for the higher chance of comorbidities in OALWH could be systematic inflammation from the HIV infection and side effects of cART (Brown et al., 2010; Gebo & Justice, 2009; Kalra & Agrawal, 2013; Spollett,

2006). There are many risk factors are associated with the diagnosis of CKD in PLWH, such as aging, hypertension, DM, nephrotoxic drugs, and hepatitis (Bonjoch et al., 2014). But the development of DM in PLWH is the main cause of CKD occurrence (Estrella & Fine, 2010).

Due to systemic inflammation, the increasing DM has become a risk factor for CKD rates (Hadigan et al., 2001). Proinflammatory cytokine (e.g., tumor necrosis factor [TNF]- α) can increase insulin resistance (Hotamisligil et al., 1996) by inhibiting insulin uptake in adipose tissue, skeletal muscles, and the liver contributing to an abnormal metabolic state (De Luca & Olefsky, 2008). Insulin resistance among PLWH is higher than in the general population because of the cART (Carr, Samaras, Chisholm, & Cooper, 1998). One of the cART, PIs, can increase the effect of glucose on insulin-responsive cells (Carr et al., 1998). Thus, using certain PIs increase insulin resistance and also leads to DM (Brown et al., 2010).

Having CKD in PLWH has increased morbidity and mortality rates when compared with PLWH without kidney disease (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004). End Stage Renal Disease (ESRD) is the end stage of renal disease, which is a reversible stage of kidney disease and where a transplant is needed (Bickel et al., 2013). It is one of the most common causes of HIV-related morbidity and mortality rates (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004). As a result, it is important to manage PLWH+DM to prevent complications, such as CKD. Still, no studies have examined the relationship between CKD occurrence and PLWH+DM.

HIV Treatment Cascade

The HIV treatment cascade, or HIV care continuum, describes the five steps for HIV care, which includes being diagnosed with HIV, linked to care, retention in care, prescribed cART, and achieved VL suppression (White House Office of National AIDS Policy, 2015). Below describe the five steps in detail (AIDS Info, 2017).

HIV Testing and Diagnosis

This is the first step to initiate the HIV treatment cascade. We can diagnose people who have HIV infection through any one of these: a confirmed HIV-positive test; detectable VL; receiving HIV-related care; have AIDS-defining illness; or receiving cART (Nosyk et al., 2014).

Linkage to Care

Linkage to care is the process of engaging a newly-diagnosed person with HIV infection into HIV primary care. PLWH who receives HIV care service will do so within 30 days of diagnosis (Nosyk et al., 2014).

Retention in Care in PLWH

Retention in care is an essential component of positive health outcomes in PLWH (Geng et al., 2010). The definition of retention in care is defined as a PLWH remaining connected to medical care, once entered (Messeri, Abramson, Aidala, Lee, & Lee, 2002). However, retention in care ends at a pre-defined interval of time after a scheduled appointment (Geng et al., 2010). Retention in care is essential components to keep receipt of cART, evaluate medication toxicity, and investigate HIV treatment failure (Geng et al., 2010). The two steps in the retention in care include starting antivirals and evaluating retention in care.

Prescribed Antivirals

The three stages in prescribed antivirals include: cART indicated; prescribed cART; and adherence to cART (Nosyk et al., 2014). cART indicated prescribed antivirals is among PLWH retained in HIV care, but not currently receiving cART yet (Nosyk et al., 2014). On cART prescribed antivirals is PLWH with cART indicated, receiving more than two antiretroviral drugs more than three months apart within one year (Nosyk et al., 2014). Adherence to cART prescribed antivirals is among PLWH on cART, receiving at least 80% adherence within one year or initiated cART within one year (Nosyk et al., 2014).

Measuring Retention in Care

Retention in care among individuals linked to HIV care is defined as those who received the CD4 cell count and VL test or received at least two antiretroviral drugs more than three months apart within one year (Nosyk et al., 2014). To be effective, cART works to generate immunological recovery and sustain virological suppression in PLWH (Alvarez-Uria, Pakam, Midde, & Naik, 2013). One of the most important aspects of care for PLWH is to initiate cART (Kinloch, Kwong, Ellis, Johnson, & Smith, 2015). The common measurement of retention in care in PLWH includes: missed visits; visit adherence; visiting gaps in care; and visiting consistency and the Health and Resources Services Administration HIV/AIDS Bureau [HRSA HAB] measure) (Mugavero, Westfall, et al., 2012).

A. Missed Visits

Missed visits is defined as the number of missed visits during the course of clinic care in a specific time period; it includes only "no-shows," not cancelled or rescheduled visits et al., 2010; Mugavero, Davila, Nevin, & Giordano, 2010; Mugavero, Westfall, et al., 2012). Many studies measured missed visits as a dichotomous variable (yes or no) (Magnus et al., 2010; Mugavero, Lin, Willig, et al., 2009; Mugavero, Westfall, et al., 2012) or a counted variable (number of missed visits) (Brennan, Maskew, Sanne, & Fox, 2010; Mugavero, Westfall, et al., 2012).

B. Visit Adherence

Visit adherence is divided into visit adherence and visit nonadherence (Mugavero et al., 2010). Visit adherence is a proportion, with the number of visits arrived for in the numerator and the number of all scheduled visits (number of arrived + number of bumped + number of no-shows) in the denominator, and it is presented as a percentage (range: 0–100%) (Catz, McClure, Jones, & Brantley, 1999; Kissinger et al., 1995; Mugavero et al., 2010; Mugavero, Westfall, et al., 2012).

C. Visiting Gaps in Care

Visiting gaps occur when patients with an HIV/AIDS diagnosis fail to keep appointments for follow-up medical visits with a provider during cART. The gaps in care are measured by a time

interval between visit constancy, visiting gaps, and the HRSA HAB measure (Fleishman et al., 2012; Mugavero et al., 2010; Mugavero, Westfall, et al., 2012).

D. Visit Consistency

Visit consistency is the proportion of at least one-time visits within the specific time intervals (Mugavero et al., 2010; Mugavero, Westfall, et al., 2012). As follow-up on the guidelines from the Panel on Antiretroviral Guidelines for Adults Adolescents (2017), the visit usually consists of an assessment duration range of every three to six months (Panel on Antiretroviral Guidelines for Adults Adolescents, 2017).

E. HRSA HAB Measure

The Health and Resources Services Administration HIV/AIDS Bureau developed the HRSA HAB measure for measuring retention in care (U.S. Department of Health and Human Services, 2016). The HRSA HAB measure identifies whether PLWH visited more than two times during 90 days within a 12-month period (Hall et al., 2012; Mugavero et al., 2010; Mugavero, Westfall, et al., 2012; U.S. Department of Health and Human Services, 2016). The numerator is the 'number in denominator who did not have a provider visit in last 6 months of review year,' and the denominator is 'one or more medical visits in first 6 months, not deceased by the end of the year, incarcerated over 90 days during the year or lost to follow-up' (Massachusetts Department of Public Health and The Boston Public Health Commission, 2013). This measure matches with the National HIV/AIDS Strategy (Health Resources Services Administration, 2008), and it captured appointment constancy and gaps in care (Mugavero et al., 2010), but there is a lack of research using the HRSA HAB measure retention in care in PLWH.

Importance of Retention in Care

Retention in care in PLWH is engaging medical care and attending required provider visits for primary HIV care (Geng et al., 2010). Retention in care has a significantly positive relationship with health outcomes, VL suppression, slower HIV progression, and reduced HIV transmission

(Giordano, Hartman, Gifford, Backus, & Morgan, 2009; Metsch et al., 2008; Mugavero et al., 2010).

Followed by the U.S. clinical practice guideline, one of the major important issues in the management of PLWH is retention in care (Panel on Antiretroviral Guidelines for Adults Adolescents, 2017). The U.S. clinical practice guidelines suggest that PLWH receive cART every three to four months (Panel on Antiretroviral Guidelines for Adults Adolescents, 2017; White House Office of National AIDS Policy, 2015). But according to the CDC, only 28% of people with HIV/AIDS have VL sustain, and 49% of people with HIV/AIDS are not engaged in constant retention in care (CDC, 2011b ; Gardner, McLees, Steiner, del Rio, & Burman, 2011).

Discontinuous retention in care in PLWH is defined as those who did not receive consistent care for their HIV that may cause a lapse cART due to an expired prescription (Mugavero, Amico, et al., 2012). Discontinuous retention in care in PLWH has a negative effect on health outcomes as a result of high VL (Mugavero, Amico, et al., 2012). Discontinues retention in care has been associated with decreases in CD4 cell count and increases in VL (Berg et al., 2005; Hogg et al., 1998; Lima et al., 2009; Mugavero, Amico, et al., 2012; Mugavero, Lin, Allison, et al., 2009; Tripathi, Youmans, Gibson, & Duffus, 2011; Walensky et al., 2006), which are ultimately significantly negative related with clinical outcomes and survival rates (Mugavero, 2008). PLWH having poor retention in care were two times more likely to die than those who received continuous retention in care (Giordano et al., 2007).

PURPOSE OF THE STUDY

This dissertation study has two goals. The first is a longitudinal retrospective cross-sectional study aim (Aim 1): to investigate retention in care between PLWH+DM divided by age groups (OALWH, YALWH) by 1) comparing paths regarding the retention in care and disease control (CD4 cell count, HbA1c level) by two age groups (OALWH, YALWH), 2) investigating variables (demographics and symptom burden) associated with retention in care. The second aim is a longitudinal retrospective comparison study aim (Aim 2): to compare the short-term health

outcomes (CKD occurrences) between PLWH and PLWH+DM groups in 2006 through 2015, and to compare the long-term health outcomes (survival rates) differences among PLWH, PLWH+DM, and PLWH+DM+CKD groups.

The specific aims of the dissertation are as follows:

Aim 1. Describe the population of OALWH+DM who visited the CNICS clinics during 2015.

Research question 1: What are the differences in demographic descriptive characteristics (age, gender, race/ethnicity) and baseline disease control (CD4 cell count, HbA1c level) between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

Research question 2: What are the differences in retention in care descriptive characteristics (missed visits, visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure) between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

Research question 3: What are the correlations between retention in care measurements (missed visits [count, dichotomous]), visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure), and each other between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

Research question 4: What are the relationships between retention in care measurements (missed visits [count, dichotomous]), visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure), and CD4 cell count between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

Research question 5: What are the differences paths in retention in care regarding HIV disease control (CD4 cell count) and DM disease control (HbA1c level) between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

Research question 6: What are the relationships between symptom burden (HIV Symptom Index) and retention in care (HRSA HAB measure) between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

Aim 2: Investigate the effect of comorbid conditions of DM and CKD on the survival rates of PLWH+CKD who visited the CNICS clinics from 2006 through 2015.

Research question 1: What are the different characteristics (age, gender, race/ethnicity, mortality, CD4 cell count, HbA1c level) among PLWH, PLWH+DM, and PLWH+DM+CKD during the years 2006—2015?

Research question 2: What is the occurrence of chronic kidney disease (CKD) among PLWH and PLWH+DM who visited the CNICS clinics in the years 2006—2015?

Research question 3: What is the 10-year survival rates among PLWH, PLWH+DM, and PLWH+DM+CKD who visited the CNICS clinics (2006—2015)?

CONCEPTUAL FRAMEWORK

For this study, the author tested a conceptual model based on the study model presented by Mugavero, Westfall, et al. (2012) for retention in care for PLWH, which involved measuring retention in HIV care in all age groups. 1) Model 1 (Figure 1) views linear causal pathways among symptom burden, retention in care, and disease control by different age groups in PLWH+DM. These causal pathways explain the effect of retention in care on disease control. At each respective point, factors represent the samples' characteristics and symptom burden, which are attributed to the retention in care, and this retention in care is in turn attributed to the disease control in different PLWH+DM age groups. 2) Model 2 (Figure 2) views linear causal pathways between CKD occurrence rate and survival rates in different disease groups. These causal pathways demonstrate the occurrence of CKD and survival rates among PLWH, PLWH+DM, and/or PLWH+DM+CKD. At each respective point, factors represent the samples' characteristics as well as any

characteristics attributed to CKD occurrences and survival rates in PLWH, PLWH+DM, and/or PLHW+DM+CKD groups.

The proposed conceptual model for this study consists of predictor variables and health outcomes. Health outcomes included both short-term and long-term effects. For Aim 1, the predictor variables included demographic (age, gender, race/ethnicity) and symptom burden (HIV Symptom Index) variables. The Aim 1 model proposed that retention in care improved disease control, e.g.., CD4 cell count, HbA1c level, both of which are short-term outcomes in PLWH+DM. Retention in care measurements included missed visits, visit adherence, visit constancy, visits gaps, and the HRSA HAB measure. To investigate the association between symptom burden and retention in care, the researcher used the HRSA HAB measure of retention. Further, the paths present relationships between retention in care measurements (missed visits [count], visit clinic attendance, visit adherence, 4-month visit constancy) and disease control (CD4 cell count, HbA1c level). Aim 2, the predictor variables, included demographics (age, gender, race/ethnicity), diagnosed disease (PLWH, PLWH+DM, PLWH+DM+CKD), age at initial CNICS clinic visits groups (≤ 30, 31-50, > 50 years old), and disease control (CD4 cell count and HbA1c levels) variables; the short-term outcomes that result are HIV and DM complications (CKD occurrence). Long-term outcomes are survival rates among PLWH, PLWH+DM, and PLWH+DM+CKD. The studies tested this model using the Center for AIDS Research (CFAR) Network of Integrated Clinic Systems (CNICS) data set, which includes data for each of the variables presented in Figure 1 and Figure 2. Although these two conceptual models have not yet been fully validated, their pathways provide a useful view of retention in care, CKD occurrence, disease controls, and survival rates.

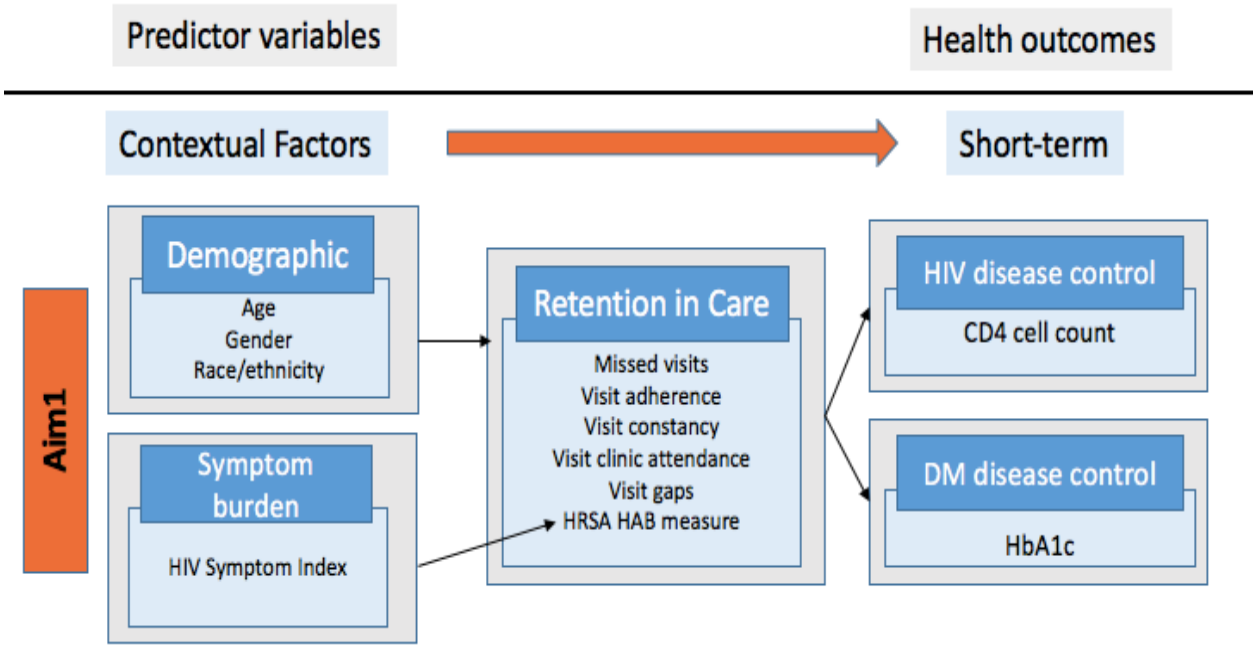

Figure 1. (Model 1) A conceptual model of retention in care for PLWH+DM

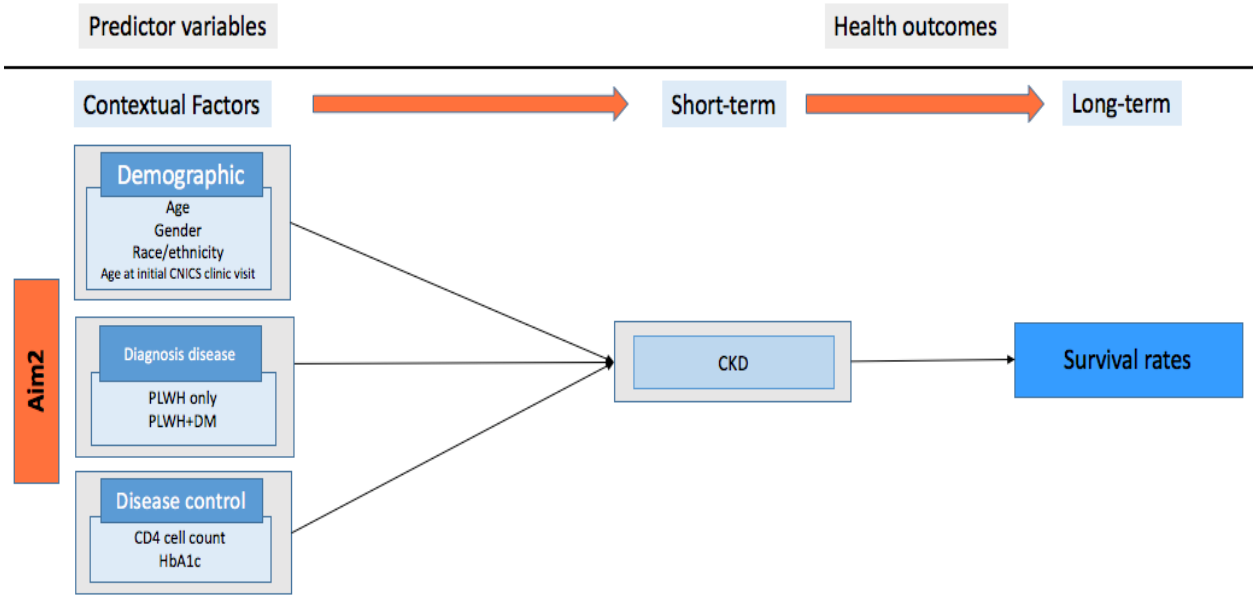

Figure 2. (Model 2) A conceptual model of CKD occurrence/survival rates for PLWH, PLWH+DM, and/or PLWH+DM+CKD

DEFINITIONS OF MAJOR CONCEPTS

The definitions of this study are presented below.

Acquired Immune Deficiency Syndrome (AIDS): Affliction among HIV-infected patients who developed stage 3 (AIDS) (CD4 cell count below 200 cells/μL) (AIDS Info, 2016e).

CD4 cell count: The study will use three categories presented in the CDC Classification System for HIV-Infected Adults and Adolescents (category 1: ≥ 500 cells/μL, category 2: 200-499 cells/μL, category 3: < 200 cells/μL) (Castro et al., 1993).

The Center for AIDS Research (CFAR) Network of Integrate Clinic Systems (CNICS): The CNICS included around 32,000 HIV-infected patients over 18 years old who visited one of the following clinics: The University of Washington; Case Western Reserve University; University of California, San Francisco; University of North Carolina at Chapel Hill; Johns Hopkins University; Fenway Health; University of California, San Diego; or University of Alabama at Birmingham. The CNICS included data from 1998 to 2015.

Chronic kidney disease (CKD): People who were diagnosed with CKD by the CNICS using the CKD-EPI equation.

Diabetes (DM): People who were diagnosed with DM by the CNICS (HbA1c level over 6.5% and/or have DM medications).

Diabetes (DM) disease control: HbA1c level is used to determine disease control in DM patients (Inada, Oishi, Nishikawa, Kurata, & Imura, 1980).

Older adults living with HIV (OALWH): People over 50 years old people who are HIV-infected (Emlet, 2006; Legarth et al., 2016; Savasta, 2004; Webel et al., 2014).

End Stage Renal Disease (ESRD): The last stage of chronic kidney disease at which people need to initiate renal replacement therapy (Bickel et al., 2013).

Hemoglobin A1c (HbA1c) level: The HbA1c level reflects the average blood glucose level during the previous two to three months (Hanas & John, 2010).

HIV-associated nephropathy (HIVAN): Kidney disease associated with HIV infection (Winston, Burns, & Klotman, 1998).

HIV disease control: The CD4 cell count is the major disease-control measurement in HIV-infected people (AIDS Info, 2016c).

HIV Symptom Index: 20-items (fatigue, fever, dizzy, neuropathy, forgetful, nausea, diarrhea, sad, anxious, sleep problems, skin problems, coughing, headache, loss appetite, bloating, muscle aches, sex problems, body fat, weight loss, hair loss) with five response choices—0: I do not have the symptom, 1: I have the symptom, but it does not bother me, 2: I have the symptom, but it bothers me little, 3: I have the symptom, and it bothers me some, 4: I have the symptom, and it bothers me a lot (Justice et al., 2001).

HIV treatment cascade care: Five steps for improving HIV care (diagnosed, linked to care, retention in care, prescribed antiretroviral therapy, and achieved VL suppression) (AIDS Info, 2017).

Mortality/Survival rates: Mortality ascertainment refers to people who have death records from the CNICS clinics, the National Death Index (NDI) and death certificate data (ICD-9 and ICD-10). Mortality rates/Survival rates were calculated as number of deaths per 100 person-years during 10-years (2006-2015).

Persons living with human immunodeficiency virus (PLWH): People who are infected with human immunodeficiency virus (CDC, 2017c).

Retention in care measurement: This measured six retention in care methods (missed visits [count, dichotomous], visit adherence, 4-month visit consistency, 6-month visit gap, and the HRSA HAB measure) (Mugavero, Westfall, et al., 2012).

- Missed visits: Counting the number of no-shows (Mugavero, Westfall, et al., 2012).
- Missed visits: Dichotomous variable (0: Always show, 1: more than one time no show) (Mugavero, Westfall, et al., 2012).
- Visit adherence: Number of arrived/Number of arrived + Number of bumped + Number of no-shows (Mugavero, Westfall, et al., 2012).
- Four-month visit consistency: Measuring four-month visit consistency (0: no 4-month visit, 1: presented 4-month visit) (Mugavero, Westfall, et al., 2012).

- Six-month visit gap: Measuring six-month visit gap (0: presented gap ≤ 188 days, 1: presented gap ≥ 189 days) (Mugavero, Westfall, et al., 2012).
- HRSA HAB measure: Had two kept visits separated by more than 90 days during the one year (0: not retained; 1: retained 90-days gap) (Mugavero, Westfall, et al., 2012; U.S. Department of Health and Human Services, 2016).

Younger adults living with HIV (YALWH): People aged 50 and under 50 years and older who are HIV-infected.

Viral load (VL): Viral load is testing how many HIV-related virus particles exist in a milliliter of a person's blood; people without HIV do not have viral load (U.S. Department of Health and Human Services, 2016).

ASSUMPTIONS

There are several assumptions for this study:

1. Data entry from the CNICS occurred without errors.

2. The conceptual frameworks are an appropriate framework to answer the research questions.

3. All participants in this study answered questions honestly and accurately.

LIMITATIONS

This study has several limitations:

1. The study findings are limited to the CNICS participants. Thus, it could have generalization problems.

2. This study's Aim 1 only considered the one-year observation period in 2015. Thus, it may not have been systematically captured.

3. This study's Aim 1 exclude the people who died during the one-year observation period from the primary analysis.

4. This study has missing data, which the author excluded. Thus, it could have bias.

SUMMARY

This chapter explained the background and significance of retention in care in HIV and survival rates in PLWH with comorbid conditions. This study has two aims. Aim 1 seeks to investigate retention in care measurements in PLWH+DM divided by different age groups, to define path differences in disease controls (CD4 cell count, HbA1c level) divided by different age groups in PLWH+DM, and to demonstrate symptom burden and retention in care in OALWH+DM and YALWH+DM. Aim 2 is to find the occurrence of CKD in two different groups (PLWH, PLWH+DM), and to investigate survival rates among PLWH, PLWH+DM, and PLWH+DM+CKD groups. Chapter Two will present the literature review. Chapter Three will present the Aim 1 study, and Chapter Four will present the Aim 2 study. Finally, Chapter Five will present the discussion, conclusions, and implications.

Chapter Two: Literature Review

In this chapter will present the overall literature review based on the Aims. This literature review will examine current research linking 1) retention in care in older adults (OA) living with human immunodeficiency virus (HIV) (LWH) with diabetes (DM), and 2) chronic kidney disease (CKD) occurrence and survival rates in PLWH. This review will provide a brief overview of OALWH. Next, it will describe retention in care and health outcomes in persons living with HIV (PLWH), comorbid conditions in PLWH+DM, a systematic review of CKD occurrence in PLWH. Lastly, it will describe the survival rates in PLWH.

OAPLWH

The number of OAPLWH is increasing (Mahy et al., 2014) from 17 % in 2001 and 31% of OA people (over 50) in 2008 had HIV infection (CDC, 2005, 2011a). About 30.4% OA diagnosed HIV infection after 50 years old (Paul, 2007). The OA population is vulnerable to acquiring HIV infection (Fox & Rosen, 2010; Micek et al., 2009). The OA have less knowledge of HIV/AIDS infections and sexually transmitted diseases (STDs) than younger people, so HIV/AIDS spread easily to the OA (Paul, 2007). Once diagnosed, OALWH have a higher chance of AIDS progression when compared to younger adults living with HIV (YALWH) (Barth, van der Loeff, Schuurman, Hoepelman, & Wensing, 2010; Rosen & Fox, 2011). Due to the decreased tendency for OA to test HIV/AIDS, so OALWH tend to undergo HIV treatments that started later (Paul, 2007). Thus, 50% of OALWH progress to acquired immunodeficiency syndrome (AIDS), which is the third stage of HIV infection, in less than one year from diagnosis (Martin et al., 2008). Also, there are racial/ethnic disparities in the HIV incidence rate among OALWH. The chance of HIV infection in OA is twelve times higher in African Americans and five times higher in Hispanics than in Whites (Kirk & Goetz, 2009).

Overall, with improved treatment, the OALWH population is steeply growing, and they have complex medical management. OA tend to have more comorbid conditions and late HIV diagnoses, and due to those late diagnoses, they have had more of a chance for disease progression

(AIDS), which is significantly correlated with mortality rates. Although OALWH need more focus care, limited studies exist in OALWH population.

Barriers to Care in OALWH

There are some barriers to HIV care in OALWH. First, it remains hard to diagnose an HIV infection in OALWH because the early symptoms of HIV are similar to aging, such as decreased immune system, fatigue, weight loss, loss of appetite, and memory loss (Simone & Appelbaum, 2008). Moreover, doctors commonly do not think OA are at risk of contracting HIV/AIDS (Myers, 2009; Schmid et al., 2009) because one of the main risk factors for transmission is being sexually active, and doctors' believe OA are not as sexually active as younger people (Lindau et al., 2007; Paul, 2007). However, OALWH, however, are more vulnerable to infection. Aging makes the immune system weaker, and a weak immune system is not able to fight off infections as well (Wooten-Bielski, 1999). Thus, with a weak immune system, OALWH rapidly progresses to AIDS (Wooten-Bielski, 1999) and causes death (Kirk & Goetz, 2009). It is therefore important to identify the HIV infection and AIDS early because effective combined antiretroviral therapy (cART) will give OALWH a chance at a longer life because the initiation of cART contributes to lower mortality rates (Moyer, 2013).

In summary, review articles on barriers to care in OALWH have stated that there are many barriers to care for this population. OA are hard to diagnose in the initial stage of HIV infections due to similar symptoms of aging. Because of this, OA have a delayed age at initial CNICS clinic visit, which makes them have higher mortality rates (Kirk & Goetz, 2009) due to disease progression (Wooten-Bielski, 1999). Despite the importance of taking care of OALWH, not many studies have focused on this population. To explore ways to improve OA's HIV care, researchers need to conduct more studies on OALWH that consider their special circumstances.

RETENTION IN CARE AND HEALTH OUTCOMES IN PLWH

Retention in care in PLWH is a priority for health care providers (Crawford, Sanderson, & Thornton, 2013). Retention in care in PLWH is quite important because it relates to positive health

outcomes; sustain viral load (VL), control CD4 cell count, and protect to HIV progression (Horstmann et al., 2010; Mugavero, Amico, et al., 2012; Mugavero et al., 2010). This becomes significantly important because it contributes to maximizing VL suppression, reducing HIV/AIDS progression, and decreasing HIV transmission (Giordano et al., 2009; Metsch et al., 2008; Mugavero et al., 2010).

CDC guideline recommended that HIV-afflicted patients receive cART following visits every three to four months (Panel on Antiretroviral Guidelines for Adults Adolescents, 2017). Nonetheless, the Yehia et al. (2012) outpatients study indicated that 58.4% PLWH had visiting gaps (N = 17,425). Among them, 31.1% PLWH had at least visiting gaps in care, in visits during seven to twelve months, and 27.7% had more than one visiting gap longer than one year (Yehia et al., 2012). Moreover, 27.2% participants did not visit at least one quarter (Yehia et al., 2012). Also, 57.4% participants did not meet the Health and Resources Services Administration HIV/AIDS Bureau (HRSA HAB] measure criterion during their outpatient time (Yehia et al., 2012). Sixty percent of PLWH had missed visit within one year (Mugavero, Lin, Willig, et al., 2009). Having missed visits within one year after initiated cART, the mortality rate was twice higher than who did not missed at all ($p < 0.02$) (Mugavero, Lin, Willig, et al., 2009). In addition, the missed visits were associated with the hazards of mortality (hazard ratio [HR]: 2.90, 95% confidence interval [CI]: 1.28-6.56). This low retention in care have possible reasons due to uninsured, substance abuse, and mental illness (Mugavero, Lin, Willig, et al., 2009).

Measuring retention in care can be done by calculating visiting times and visiting intervals (Mugavero, Westfall, et al., 2012). Even so, several studies have suggested that the standard of retention in care in PLWH would include missed visits, visit adherence, visit constancy, visiting gaps, and the HRSA HAB measures (Health Resources Services Administration, 2008; Mugavero et al., 2010; Mugavero, Westfall, et al., 2012; Yehia et al., 2012). Among 10,053 participants, all of the six retention in care measurements associated significantly with missed visits (odds ratio [OR] 0.73, 95% CI: 0.71-0.75), visit adherence (OR: 3.9, 95% CI: 3.5-4.3), visit constancy (OR:

2.8, 95% CI: 2.5-3.0), visiting gaps (OR: 3.0, 95% CI: 2.6-3.3), and the HRSA HAB measure (OR: 3.8, 95% CI: 3.3-4.4) (Mugavero, Westfall, et al., 2012).

In sum, the previous studies demonstrated that retention in care is one of the key components (Geng et al., 2010) to positive health outcomes in PLWH (Horstmann et al., 2010; Mugavero, Amico, et al., 2012; Mugavero et al., 2010). Many studies did not use the same methods to measure retention in care in PLWH, but, usually, studies commonly used missed visits, visit adherence, visit constancy, and visiting gaps to measure retention in care in PLWH. However, in addition to the importance of retention in care in PLWH, previous studies indicated that we need to take care of OALWH who have comorbid conditions. However, there are no studies regarding retention in care of OALWH with comorbid conditions, including DM and CKD. In sum, healthcare professionals need more research on retention in care in OALWH who have comorbid conditions.

COMORBID CONDITIONS IN PLWH +DM

Having comorbid conditions depend on age, HIV stage, and severity (CD4 cell count, VL) ($p < 0.001$) (Goulet et al., 2007). Sixty percent of PWLH (N = 33,420) had at least one comorbid condition ($p < 0.001$) (Goulet et al., 2007). Another study indicated that 60% of OALWH who were over 50 have a comorbid condition (Rolls et al., 2014). The Goulet et al. (2007) study is a large cohort study that compared comorbid conditions among veterans (HIV infection n = 33,420, without HIV infection n = 66,840). The most frequent comorbid conditions were hypertension (20%), DM (8%), vascular diseases (6%), liver diseases (13%), and renal diseases (3%) ($p < 0.001$) in PLWH (Goulet et al., 2007). Also, PLWH had increased chances to have comorbid conditions of renal, vascular, and pulmonary diseases than the population without HIV infection (Goulet et al., 2007). Additionally, 31% of PLWH were OA and they have more multimorbidity conditions than OA without HIV infections ($p < 0.001$) (OR: 1.17, 95% CI: 1.02-1.33) (Goulet et al., 2007). In the Magalhães, Greenberg, Hansen, & Glick (2007) study, 88.8% (N = 162) OALWH had at least one comorbid condition; 18% PLWH had one comorbid condition, 27.8% had two, and more

than a half-percent of people had more than three comorbid conditions. Further, aging and HIV infection were significantly close relationships on DM occurrence (OR: 1.12, 95% CI: 1.02-1.03), vascular diseases occurrence (OR: 1.12, 95% CI: 1.00-1.24), and liver diseases occurrence (OR: 1.29, 95% CI: 1.16-1,44) (Goulet et al., 2007). Through the previous studies, we can ascertain that most OALWH had comorbid conditions. The need exists to focus on DM because it is one of the primary comorbid conditions occurring in OALWH (Vance, Mugavero, Willig, Raper, & Saag, 2011). The most frequent comorbid conditions according to the Goulet et al. (2007) study, hypertension, and DM is the major risk factor of occurring hypertension. Incidentally, the medical field regards DM as a chronic disease that is defined as manageable (Ross, 2004). The most important reason to express concern about DM is that chronic diseases correlate highly with non-HIV-related death rates (Braithwaite et al., 2005), so by addressing DM in PLWH, we can expect an improvement in health outcomes in PLWH. However, previous studies have not evaluated and compared PLWH and PLWH+DM. Therefore, we need to conduct research on comorbid conditions, especially on DM in PLWH, to define their unique characteristics.

PLWH+DM

With expanded access to cART today, the prevalence of PLHW with DM as a comorbid condition is increasing (Isa et al., 2016); for instance, 5% of 1,000 people who received cART have DM (Riyaten et al., 2015). The mortality rate of PLWH+DM was 24.4% within a 95% CI = 4.46–5.00 ($p < 0.05$) in 1991 through 2011 (Moreira et al., 2016). HIV with cART carries a risk factor of DM (Brar, Shuter, Thomas, Daniels, & Absalon, 2007; De Wit et al., 2008; Galli et al., 2012; Isa et al., 2016; Samaras, 2009; Shen et al., 2013). HIV infection causes insulin resistance and peripheral lipodystrophy (Rudich, Ben-Romano, Etzion, & Bashan, 2005). cART includes protease inhibitor (PI) medications such as tenofovir, which causes insulin resistance and dyslipidemia (Grinspoon & Carr, 2005; Rudich et al., 2005; Samaras, 2009), which prevents the uptake of glucose and interferes with adipogenesis, adipocytes, and hepatocytes (Rudich et al., 2005). Further, having DM is closely related with aging, just as it is in the general population (Brar

et al., 2007). In a large cohort study in PLWH, the prevalence of DM in PLWH baseline was 2.3% (Isa et al., 2016), and it is closely related with aging. The incidence of DM when they received cART was 5.3%–6.0% (Dever, Oruwari, Figueroa, O'Donovan, & Eng, 2000; Isa et al., 2016). About 5.3% had newly diagnosed DM after received cART for one year (95% CI, 4.2%-6.3%) (Isa et al., 2016).

Empirical research has demonstrated that, due to aging, HIV infection, and HIV treatments, PLWH are more likely to develop DM. DM is one of the most common chronic diseases in PLWH, and having a chronic disease is a major non-HIV-induced reason for death in PLWH (Braithwaite et al., 2005). Having more comorbid conditions causes patients to carry more of symptom burden and results in negative health outcomes in PLWH (Gay et al., 2011; Gonzalez et al., 2007; Harding et al., 2012; Holzemer, Hudson, Kirksey, Jane Hamilton, & Bakken, 2001; World Health Organization, n.d.). The settings and populations in previous studies were very limited, however, and few studies demonstrated the prevalence of DM in PLWH, and there are no comparison studies in PLWH and DM. For future studies, we need to focus on the comparison between PLWH and PLWH+DM based on their different characteristics and a focus on their health outcomes.

THE PREVALENCE OF CHRONIC KIDNEY DISEASE IN PERSONS LIVING WITH HIV: A SYSTEMATIC REVIEW

Abstract

Objective: A systematic review of the research on chronic kidney disease (CKD) in persons living with human immunodeficiency virus (HIV) (PLWH), in order to (1) examine studies' characteristics, (2) define estimated glomerular filtration rate (eGFR) used to determine CKD, (3) identify risk factors for CKD, and (4) investigate CKD's prevalence in PLWH.

Methods: Keyword searches of the PubMed and PsycInfo databases and manual searches of references for 2000 through 2016, following PRISMA guidelines. Articles that presented the prevalence of CKD in people with HIV were selected.

Results: Twenty-one studies met inclusion criteria. The prevalence of CKD in those with HIV ranged from 2.3% to 53.3% across a variety of countries. The most common equation for obtaining eGFR was modification of diet in renal disease (MDRD), and most articles used the CKD criterion of eGFR < 60 mL/min/1.73 m^2 and/or presence of protein in the urine. Major risk factors for CKD in PLWH were related to hypertension, diabetes (DM), and age.

Conclusion: Further research needs to be done to determine why we have such a wide prevalence range.

Keywords: chronic kidney disease; HIV; prevalence; systematic review

Introduction

Over one million Americans have human immunodeficiency virus (HIV) (CDC, 2017b). Since the development of combined antiretroviral therapy (cART), the life expectancy of persons with HIV has increased (Althoff et al., 2015; Joint United Nations Programme on HIV/AIDS, 2013; Samji et al., 2013) such that they can expect to live about early 70 years, which is similar to the expected age of the general population (Nakagawa et al., 2012). With longer life spans, however, PLWH are developing other chronic medical conditions (Cailhol et al., 2011; Calza et al., 2014; Campbell et al., 2009; Winston, 2010). In the U.S., for example, it has been estimated that approximately 70% of PLWH have polymorbidity (Buchacz et al., 2013). This may be related to the negative side effects of cART, which include dyslipidemia (Buchacz et al., 2013; Cao et al., 2013; Cheung et al., 2007; Fernando, Finkelstein, Moore, & Weissman, 2008), nephrotoxicity, and kidney stone formation (Izzedine, Harris, & Perazella, 2009).

One of the most commonly diagnosed chronic diseases in PLWH is chronic kidney disease (CKD) (Naicker, Rahmanian, & Kopp, 2015). CKD is the irreversible destruction of the functional units of the kidney, or nephrons, which clean waste from the body and produce urine (Naftalin,

Nathan, Hamzah, & Post, 2011). If CKD is uncontrolled, irreversible damage to the kidneys will ultimately require dialysis (Gardner et al., 2003; Gupta et al., 2004).

Many factors are associated with the development of CKD in PLWH, including hypertension, diabetes (DM), HIV treatments, African American race, and old age (Bonjoch et al., 2014; Izzedine et al., 2009; Kopple, 2001; Naftalin et al., 2011; Naicker et al., 2015; Szczech et al., 2002; Winston, 2010). The relationship between hypertension and kidney disease has not yet been identified (Peck et al., 2014). The only known of currently, kidney disease is a secondary hypertension complication in PLWH (Peck et al., 2014). PLWH+DM tend to have more albuminuria than PLWH alone (48.0% vs. 33.3%, $p < 0.05$) in 2007 (Cohen et al., 2010), and albuminuria affects negative viral load (VL) suppression (Kim et al., 2011). HIV treatment, or cART, especially with tenofovir, affects the estimated glomerular filtration rate (eGFR) (Horberg et al., 2010) and can cause renal tubular dysfunction (Hall, Hendry, Nitsch, & Connolly, 2011). As CKD is a risk factor for end stage renal disease (ESRD) and death (Choi et al., 2010; Ibrahim et al., 2012), early identification of CKD can prevent or reduce the risk of complications such as kidney disease progression and cardiovascular events (Choi et al., 2010; Ibrahim et al., 2012). Current clinical guidelines suggest three- to six-month regular screenings using the eGFR (Asboe et al., 2012; Kopple, 2001; Winston, 2010).

The purpose of this systematic review is to synthesize current research on CKD in PLWH. The specific aims are as follows: (1) to examine studies' characteristics, (2) to explore eGFR used to define CKD, (3) to identify risk factors for CKD in PLWH, and (4) to investigate the prevalence of CKD in PLWH.

Methods

Search Strategy

A systematic literature searches of studies from January, 2000 to August, 2016 was conducted in the PubMed and PsycInfo databases, using the following search terms: *incidence, prevalence, diabetes, diabetes mellitus, renal failure, renal disease, chronic kidney disease, CKD,*

kidney disease, HIV, AIDS, and human immunodeficiency virus. This search was supplemented by a manual search of relevant reference lists. Data extraction occurred as follows (see Figure 3). The initial database searches identified 1,960 citations in PubMed and 5,356 citations in PsycInfo, and the manual search of references found an additional 27. These citations were screened for duplicates, which were discarded, leaving 437. Titles and abstracts of the 437 articles were screened, and citations were excluded if articles were not written in English, not related to HIV-infected people, or not related to those with CKD, and also if participants were not adults over 21 years old; 61 articles then remained. These were then retrieved and reviewed in full; 21 articles from the database search were then excluded according to the following criteria: they did not address the prevalence of CKD in those with HIV; they were reviews, meta-analyses, or editorials; they presented acute kidney disease; or participants were pregnant women. In addition, 19 articles from the manual reference search were also excluded after applying the inclusion and exclusion criteria, leaving 21 studies for systematic review. Table 1 presents characteristics for CKD in PLWH in the reviewed studies.

Results

Study Characteristics

The number of participants in the 21 reviewed articles ranged from 163 to 15,135 and represented diverse ethnicities or races (White, African American, Asian, etc.) and countries of origin. Seven articles (33.3%) were conducted in the U.S., and the remaining 14 studies (66.7%) were conducted in Asia, Africa, Europe, Israel, and Argentina. The total number of PLWH across the 21 studies was 43,215. Fourteen of the studies were cross-sectional (Ayokunle et al., 2015; Bonjoch et al., 2014; Burkhalter, Sannon, Mayr, Dickenmann, & Ernst, 2014; Cailhol et al., 2011; Calza et al., 2014; Campbell et al., 2009; Cao et al., 2013; Cheung et al., 2007; Fernando et al., 2008; Hsieh et al., 2015; Okafor, Unuigbe, & Chukwuonye, 2016; Overton, Nurutdinova, Freeman, Seyfried, & Mondy, 2009; Sorlí et al., 2008; Wyatt et al., 2007), 6 were cohort studies (Berg et al., 2005; Choi et al., 2007a; Choi, Shlipak, Hunt, Martin, & Deeks, 2009; Lucas et al.,

2008; Mocroft et al., 2007; Mocroft et al., 2010; Zachor et al., 2016), and 1 was a case study (Obirikorang, Osakunor, Ntaadu, & Adarkwa, 2014). We extracted the prevalence of CKD from all studies.

Estimated Glomerular Filtration Rate (eGFR) in PLWH

Several assessments were used to define CKD in PLWH. All of the articles used an eGFR of < 60 mL/min/1.73 m^2. Equations for eGFR are used to index kidney function (Levey et al., 2009). In the reviewed studies, three eGFR equation models were used to determine CKD in PLWH. Nineteen studies used the equation for modification of diet in renal disease (MDRD), 4 studies used the CKD epidemiology collaboration (CKD-EPI) equation, and 4 studies used the Cockcroft-Gault creatinine clearance (CG) equation (see Table 2). Six studies used two equation models rather than one: three used MDRD and CKD-EPI (Bonjoch et al., 2014; Obirikorang et al., 2014; Zachor et al., 2016), and three used MDRD and CG (Cailhol et al., 2011; Mocroft et al., 2007; Sorlí et al., 2008).

It is possible that a person would be classified as having CKD by one model but not by another. The CG equation is not recommended for clinical use because its non-standardized creatinine assays can overestimate kidney function (Stevens et al., 2009). Nowadays, the CKD-EPI and the MDRD equations use standardized creatinine values because accurate creatinine level can determine kidney functions and will be used in determining drug doses, so we can prevent drug toxicity with accurate levels (Stevens et al., 2009). However, there is known systematic bias in the original MDRD model, owing that it was developed in a population of only persons with CKD. To reduce systematic bias of the MDRD, the CKD-EPI was developed using people without CKD which corrected for bias by increasing the variability (Levey & Stevens, 2010).

Prevalence of CKD in PLWH

Of the 43,215 PLWH across the 21 studies, 3,228 (7.5%) had CKD. The reported prevalence of CKD in PLWH ranged from 2.3% to 53.3%. The African American population had the highest prevalence (53.3%) (Okafor et al., 2016); the South African population had the lowest

(2.3%) (Zachor et al., 2016). In the U.S., the prevalence of CKD in PLWH ranged from 3.0% to 23.7%. Table 1 presents the prevalence of CKD differentiated by population, study area, and study characteristics. Because the prevalence is highly varied, healthcare providers may need to take the characteristics of their population, including its location, into account when deciding whether or not to screen for CKD. Screening may need to be done more often depending upon the patient demographics.

Risk factors for CKD in PLWH

The risk factors for CKD in PLWH cited most often consisted of medication (total n = 13 studies; tenofovir n = 6, indinavir n = 2, stavudine, nonsteroidal anti-inflammatory drugs [NSAIDS], aminoglycoside, drug toxicity, injection drug use n =1), hypertension (n = 12), older age (n = 9), DM (n = 8), hepatitis infection (n = 7), low level of CD4 cell count (n = 6), and race (n = 4) (see Table 3). Six studies cited tenofovir as a risk factor. Hepatitis C infection was cited more than the risk of hepatitis B (5 vs. 2 studies). Other risk factors were VL (n = 4), hyperlipidemias (n = 3), gender (n = 3), presence of proteinuria (n = 2), atherosclerosis (n = 1), and lipoatrophy (n = 1). Many risk factors, such as gender and race, are not mutable or may be caused by HIV or its treatment (glucose intolerance, lipodystrophy).

Discussion

The equation models used to eGFR differ, and each model has limitations. The MDRD equation was used most often to obtain eGFRs, but the MDRD cannot be used for people younger than 18 or older than 70 (National Institute of Diabetes and Digestive and Kidney Diseases, n.d.). This is important, because the average age of PLWH is increasing. Results differed depending on the equation used to obtain an eGFR (Van Pottelbergh et al., 2014). One study (Levey et al., 2009) indicated that the CKD-EPI equation is more accurate in diagnosing CKD than the MDRD equation, because the CKD-EPI has less bias and yields fewer median differences in eGFR than the MDRD, especially when eGFR is greater than 60mL/min/1.73m^2. To determine the extent of

kidney damage and function and inform decisions about care, we need a standard equation model for eGFR that is appropriate for an aging population.

The evidence from the 21 articles reviewed here indicates that there is an increased prevalence of CKD in PLWH as opposed to those without HIV. The broad 2.3% to 53.3% prevalence range for CKD in PLWH reflects differences in population size, region, race or ethnicity, and study characteristics. The study with the highest rate (53.3%) was conducted in South Nigeria, whose population consists of black people (Okafor et al., 2016) who have a genetic predisposition to CKD. African Americans with HIV have a higher chance of developing CKD than those of other ethnicities (Wyatt et al., 2007). As stated above, providers should consider the population when making decisions to screen for CKD.

The most severe risk factor for CKD in PLWH was medication, especially given the extensive use of tenofovir (Labarga et al., 2009). Using tenofovir causes nephrotoxicity (Fux, Christen, Zgraggen, Mohaupt, & Furrer, 2007), renal injury, proximal renal tubulopathy, and reduced eGFR (Cooper et al., 2010; Horberg et al., 2010). Therefore, medical providers need to be especially diligent in monitoring kidney damage once a patient has been placed on combined antiretroviral therapy.

Conclusion

CKD is one of the most significant comorbid conditions for PLWH. The mortality rates for CKD in PLWH is higher than in those without HIV(Choi et al., 2007b). The range for the prevalence of CKD in PLWH is wide. Uniform use of the CKD-EPI as the assessment for CKD would increase the accuracy of CKD diagnosis.

Strengths and Limitations

This systematic review of the existing studies regarding the prevalence of CKD in PLWH is comprehensive, but the varying prevalence of CKD in the studies may limit the generalizability of the review's findings.

Conflicts of interest

There were no conflicts of interest.

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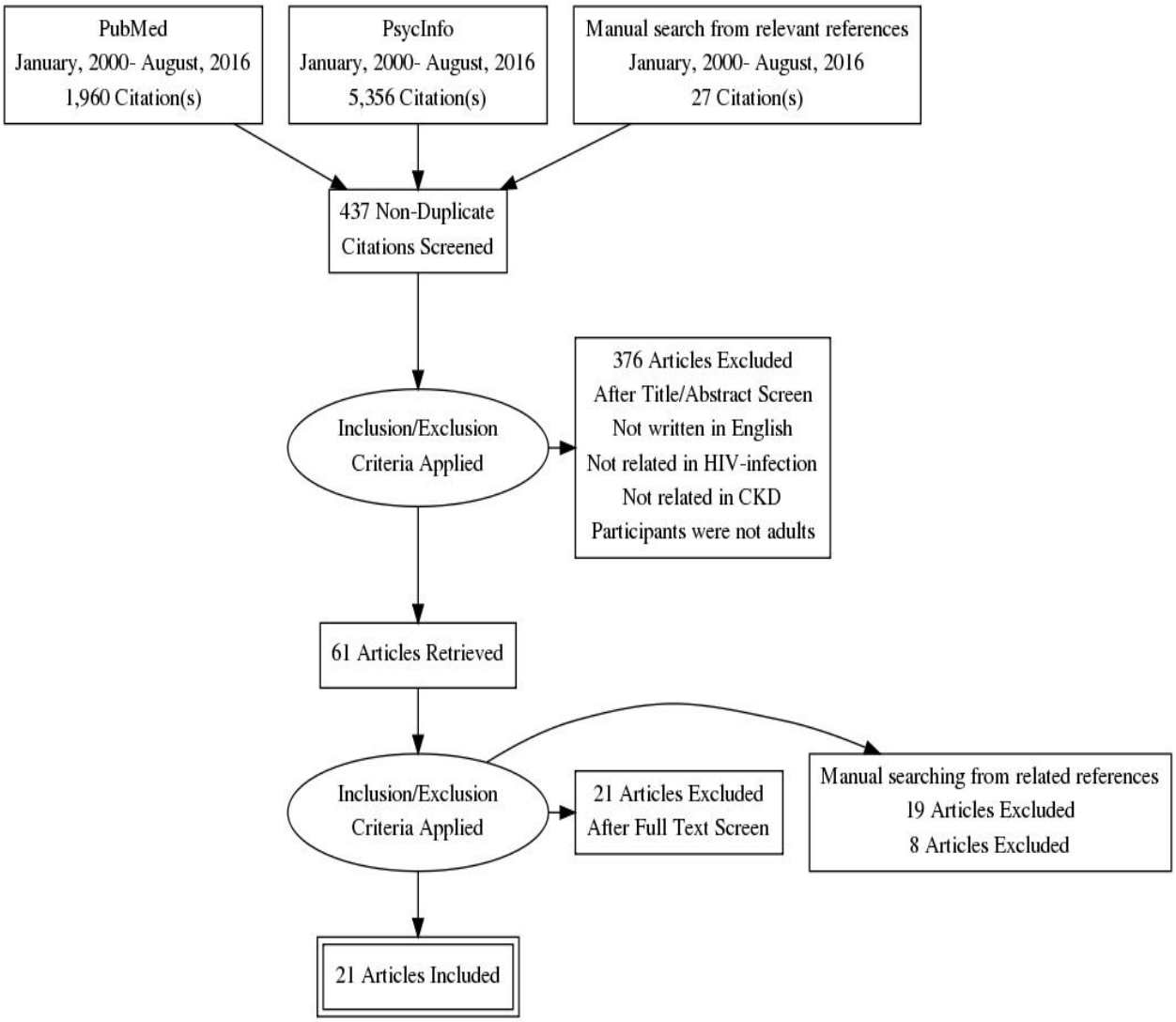


Figure 3. Search Flow chart using the PRISMA guideline (http://prisma.thetacollaborative.ca)

Table 1. Chronic Kidney Disease (CKD) in HIV-infected individual characteristics.

Study	Origin	n*	CKD criteria	CKD prevalence in PLWH N (%)	CKD risk factors in PLWH	Research Design	Biomarker
Ayokunle et al. (2015)	Nigeria	227	eGFR ≤ 60ml/min/1.73m^2, and/or ACR ≥ 30mg/g	108 (47.6)	Low CD4	Cross-sectional	MDRD
Bonjoch et al. (2014)	US	970	eGFR < 60ml/min/1.73m^2 UPC or UAC ratio	29 (3)	HTN, Age, Tenofovir	Cross-sectional	MDRD CKD-EPI
Burkhalter et al. (2014)	Haiti	164	eGFR < 90ml/min/1.73m^2, and/or proteinuria by dipstick test	5 (3.1)	None	Cross-sectional	CKD-EPI
Cailhol et al. (2011)	Burundi	300	eGFR < 60ml/min/1.73m^2, and/or kidney damage defined as a urinary abnormality at any eGFR level	137 (45.7)	DM, HTN, HBV, HCV, Aminoglycoside NSAIDS	Cross-sectional	MDRD Cockcroft-Gault
Calza et al. (2014)	Italy	894	eGFR < 90ml/min/1.73m^2, and/or renal damage or eGFR < 60ml/min/1.73m^2≥ 3 months	190 (21.3)	Age, Male, HTN, DM, Proteinuria, Hyperlipidemias (Hypertriglyceridemia), Low CD4, Tenofovir, AA	Cross-sectional	MDRD
Campbell et al. (2009)	UK	3,439	eGFR < 60ml/min/1.73m^2 ≥ 3 months, the severity of CKD categorized as stage 3-5	81 (2.4)	DM, HTN, Atherosclerosis, Drug toxicity	Cross-sectional	MDRD

Table 1. Continued

Study	Origin	n*	CKD criteria	CKD prevalence in PLWH N (%)	CKD risk factors in PLWH	Research Design	Biomarker
Cao et al. (2013)	China	538	eGFR < 60ml/min/1.73m^2, and/or isolated proteinuria ≥ 1+ on urine epipstick ≥ 3 months	86 (16)	Age, HTN, HCV, VL	Cross-sectional	MDRD
Cheung et al. (2007)	China	322	eGFR < 60ml/min/1.73m^2 or Proteinuria more than 3 months (PR/CR > 0.3g/g)	54 (16.8)	Age, HTN, DM, Indinavir, Low CD4, VL	Cross-sectional	MDRD
Choi et al. (2007b)	US	15,135	eGFR ≤ 60ml/min/1.73m^2	1,075 (7.1)	Age, HTN, HCV, VL	Cohort	MDRD
Choi et al. (2009)	US	615	eGFR < 60ml/min/1.73m^2	45 (7.8)	Female, DM, Hyperlipidemia	Cohort	MDRD
Fernando et al. (2008)	US	422	eGFR < 60ml/min/1.73m^2	100 (23.7)	HTN, DM, AA	Cross-sectional	MDRD
Hsieh et al. (2013)	Taiwan	512	ACR≥ 30mg/g and/or a protein≥ 1+ on urine examination, and/or eGFR < 60ml/min/1.73m^2 ≥ 3months	36 (7.03)	DM, HTN, Hyperlipidemias (Hypercholesterolemia)	Cross-sectional	MDRD
Lucas et al. (2008)	US	4,227	eGFR < 60ml/min/1.73m^2 ≥ 3 months	284 (6.7)	DM, HTN, HBV, Injection drug use, HCV, AA	Cohort	MDRD

Table 1. Continued

Study	Origin	n*	CKD criteria	CKD prevalence in PLWH N (%)	CKD risk factors in PLWH	Research Design	Biomarker
Mocroft et al. (2010)	EuroSIDA	6,843	eGFR < 60ml/min/1.73m^2	281 (4.1)	Tenofovir	Cohort	Cockcroft-Gault
Mocroft et al. (2007)	EuroSIDA	4,474	eGFR < 60ml/min/1.73 m^2	157 (3.5)	Age, Low CD4, Indinavir, Tenofovir	Cohort	Cockcroft-Gault MDRD
Obirikorang et al. (2014)	Ghana	163	eGFR < 60ml/min/1.73m^2	16 (9.9)	None	Case control	MDRD CKD-EPI
Okafor et al. (2016)	South Nigeria	382	eGFR < 60ml/min/1.73 m^2 ACR ≥ 200mg/g	204 (53.3)	None	Cross-sectional	MDRD
Overton et al. (2009)	US	845	eGFR < 60ml/min/1.73 m^2	68 (8)	Low CD4, HTN, proteinuria, Tenofovir, Stavudine, VL	Cross-sectional	MDRD
Sorlí et al. (2008)	Spain	854	eGFR < 60ml/min/1.73 m^2	65 (7.6)	Age, Female, Lipoatrophy	Cross-sectional	Cockcroft-Gault MDRD
Wyatt et al. (2007)	US	1,239	eGFR < 60ml/min/1.73 m^2, and/or proteinuria >100mg/dl	192 (15.5)	Age, AA, HCV, Low CD4	Cross-sectional	MDRD
Zachor et al. (2016)	South Africa	650	eGFR < 60ml/min/1.73 m^2	15 (2.3)	HTN, Age, Tenofovir	Cohort	CKD-EPI MDRD

*: Number of participants who have HIV

Notes. AA, African American; ACR, albumin creatinine ratio; CKD-EPI, chronic kidney disease epidemiology collaboration equation; DM, diabetes; eGFR, (estimated) glomerular filtration rate; HTN, hypertension; MDRD, modification of diet in renal disease equation; UAC, urinary albumin: creatinine; UPC, urinary protein: creatinine; VL, viral load

Table 2. eGFR Equations

Biomarker	Equation[‡]	CKD criteria
MDRD (Ayokunle et al., 2015; Bonjoch et al., 2014; Cailhol et al., 2011; Calza et al., 2014; Campbell et al., 2009; Cao et al., 2013; Cheung et al., 2007; Choi et al., 2007b, 2009; Fernando et al., 2008; Hsieh et al., 2013; Lucas et al., 2008; Mocroft et al., 2007; Obirikorang et al., 2014; Okafor et al., 2016; Overton et al., 2009; Sorlí et al., 2008; Wyatt et al., 2007; Zachor et al., 2016)	eGFR (mL/min/1.73 m^2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American)	eGFR < 60 mL/min/1.73 m^2 The equation has not been validated in patients older than 70.
CKD-EPI (Bonjoch et al., 2014; Burkhalter et al., 2014; Obirikorang et al., 2014; Zachor et al., 2016)	eGFR = 141 × min (Scr/$\varkappa$, 1)α × max(Scr/$\varkappa$, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if African American]	This equation provides a more accurate estimation than the MDRD.
Cockcroft-Gault (Cailhol et al., 2011; Lucas et al., 2008; Mocroft et al., 2007; Sorlí et al., 2008)	Men = (140 - age) x ideal weight 0.814 x [serum creatinine] Women = 0.85 x creatinine clearance in men	Used in clinical practice to guide dose reductions of renal excreted drugs.

*: References cited may duplicate studies.
[‡]: This equation comes from Levey et al. (2009): Scr. serum creatinine in mg/dL; $\varkappa$ .0.7 for females and 0.9 for males; α. -0.329 for females and -0.411 for males; min. the minimum of Scr /$\varkappa$ or 1; max. the maximum of Scr /$\varkappa$ or 1.
Notes. CKD-EPI, chronic kidney disease epidemiology collaboration equation; eGFR, (estimated) glomerular filtration rate; MDRD, modification of diet in renal disease equation.

Table 3. Risk Factors for CKD in PLWH

CKD risk factors in PLWH	n*	CKD risk factors in PLWH	n*
Hypertension	12	Medication – Stavudine	1
Diabetes	8	Medication – NSAIDS	1
Race: African American	4	Medication – Aminoglycoside	1
Hyperlipidemias	3	Medication – Drug toxicity	1
Older age	9	Medication – Injection drug use	1
Low CD4 cell count	6	Atherosclerosis	1
Gender – Male	1	Viral load	4
Gender – Female	2	HBV	2
Presence of proteinuria	2	HCV	5
Medication – Tenofovir	6	Lipoatrophy	1
Medication – Indinavir	2	Not indicated	3

*: References cited may duplicate studies.
Notes. HBV, hepatitis-B virus; HCV, hepatitis-C virus; NSAIDS, nonsteroidal anti-inflammatory drugs.

SURVIVAL RATES IN PLWH

Due to the development of cART, survival rates of PLWH are longer than before (Alter, 2006; Poorolajal, Hooshmand, Mahjub, Esmailnasab, & Jenabi, 2016). In addition, cART has reduced the number of HIV- and AIDS-related deaths by 2.5 million in low- and middle-income countries since 1995 (Venegas et al., 2008), and it has increased the number of survival years from 10–12 years to 25 years in PLWH (Alencar, Duarte, & Waldman, 2014; Kee et al., 2009). cART makes PLWH increase their CD4 cell count (Mills et al., 2008) and strengthens their immune systems (Poorolajal et al., 2016), which prevents the disease's progression (Mills et al., 2008). However, since HIV infection was defined, approximately 75 million people have gotten HIV infection and about 36 million people have died from issues related to HIV infection (Poorolajal et al., 2016).

One study (N = 585) from Iran figured out the survival rates divided into one-year, five-year, and ten-year categories (Mirzaei, Poorolajal, Khazaei, & Saatchi, 2013). The one-year survival rate was 87%, five-year survival rate was 67%, and ten-year survival rate was 40% (Mirzaei et al., 2013). Also, the HR between mortality related to AIDS causes was 4.77 ($p < 0.001$) among those who did not receive cART (Mirzaei et al., 2013). The other study, the meta-analysis study (N = 27,862) pointed out that in those who received cART, the survival rates at 2, 4, 6, 8, and 10 years were 87%, 86%, 78%, 78%, and 61%, respectively, while in those who did not receive cART, the survival rates at 2, 4, and 6 years were 48%, 26%, and 18%.

To conclude, those previous studies pointed out that PLWH who receive cART have higher survival rates than PLWH who do not receive cART. It is thus important to receive cART in PLWH to increase the survival rates. The other study also pointed out that due to development of cART, PLWH are getting older and have a higher chance of developing chronic diseases, which then cause an increase in non-HIV-related mortality rates (Braithwaite et al., 2005; Weber et al., 2013). As such, it is important to take care about mortality rates in PLWH with comorbid conditions. However, there are no studies on survival rates of PLWH with comorbid conditions. Therefore, we need more research on survival rates in PLWH with comorbid conditions.

SUMMARY

Research on retention in care in OALWH+DM is significantly important because previous studies have emphasized that the OALWH population is increasing significantly, and they have more of a chance to develop comorbid conditions such as DM and CKD. Retention in care is closely related with health outcomes in PLWH. However, as of the current study, there is no gold standard method of measuring retention in care in OALWH+DM, so this study will serve as a guideline of retention in care in OALWH+DM. In addition, the common complication of PLWH+DM is CKD and CKD is highly correlated with mortality rates. But no studies have considered both DM and CKD in PLWH, so this dissertation will serve as a guideline of CKD occurrence and mortality rate in PLWH with comorbid conditions in the future.

Chapter Three: Retention in Care and Symptom Burden in Persons living with HIV with Diabetes for Adults over 50

ABSTRACT

Background: Many people in the United States suffer with a human immunodeficiency virus (HIV) infection. Diabetes (DM) is the second most common comorbid condition among persons living with HIV (PLWH). The key to successful HIV management is retention in care. The purpose of this study is to investigate the relationships of retention in care measurements in PLWH+DM by age groups and relationships between symptom burden and retention in care PLWH+DM by age groups.

Methods: This is a secondary data analysis from the Center for AIDS Research (CFAR) Network of Integrate Clinic Systems (CNICS), which includes in more than 32,000 PLWH. We measured the retention in care in PLWH+DM during calendar year 2015 who visited CNICS clinic at least once. Six retention in care measurements for PLWH+DM were defined: missed visits (count, dichotomous); visit adherence; 6-month gap; 4-month visit constancy; and the Health and Resources Services Administration HIV/AIDS Bureau (HRSA HAB) measure retention in care measurement. We conducted Spearman correlation coefficients and logistic regression to investigate measurements in PLWH+DM, as well as multi-group path analysis for comparing retention in care in PLWH+DM. For investigating relationships between symptom burden (HIV Symptom Index) and retention in care, we conducted logistic regression for PLWH+DM by age groups.

Results: A total of 798 samples have PLWH+DM in calendar year 2015. Those older adults (OA) PLWH+DM had 564 samples and younger adults (YA) PLWH+DM had 234 samples. Most of the retention in care in PLWH+DM measurements were significantly correlated ($p < 0.05$). Only 4-month visit constancy was not correlated. Except missed visits (count) in OALWH+DM, no significant relationship exists between retention in care measurements CD4 cell count using logistic regression. But multi-group path analysis demonstrated that CD4 cell count had significant relationships with most retention in care measurements in all age groups. Still, hemoglobin A1c

(HbA1c) level was the only significant relationship with most of retention in care measurements in YALWH+DM. As for symptom burden, significant relationships took place with symptom burden (fatigue, sadness, memory loss) and retention in care in OALWH+DM.
Conclusion: The results showed that retention in care have relationships with disease control (CD4 cell count, and HbA1c level) in PLWH+DM, and notably, HbA1c level was only significantly affected by YALWH+DM. In future research, we need to find more accurate reasons why the HbA1c level only significantly relationships with YALWH+DM. This study can contribute to guide research on PLWH+DM in the future.

Keywords: CD4 cell count, diabetes, Hemoglobin A1c, HIV, retention in care

INTRODUCTION

Overall, 1.2 million people in the United States are suffering from an HIV (CDC, 2017b). Due to the development of the combined antiretroviral therapy (cART), the life expectancy of persons living with human immunodeficiency virus (HIV) (PLWH) has extended to the early 70s, which comparable to the general population's life expectancy (Antiretroviral Therapy Cohort Collaboration, 2008; Samji et al., 2013). As PLWH aging, however, more than half have at least one comorbid condition (Rolls et al., 2014). Diabetes (DM) is one of the most common comorbid conditions (Brown et al., 2005; Butt et al., 2009; Medapalli et al., 2012) among PLWH over 50 years old (Vance et al., 2011) and 10 to 15% of PLWH have DM (Brown et al., 2010; Butt et al., 2009). A recent study indicated that PLWH have higher chance of developing DM than their seronegative counterparts (Brown et al., 2010; Butt et al., 2009; De Wit et al., 2008). One of the most common reasons for PLWH developing DM is due to the combined antiretroviral therapy's (cART) adverse effects (Brown et al., 2005; De Wit et al., 2008; Kim et al., 2011; Ledergerber et al., 2007). The cART promotes the glucose intolerance (Brown et al., 2005; De Wit et al., 2008; Kim et al., 2011; Ledergerber et al., 2007). One of the cART, HIV-1 protease inhibitors (PIs),

increases insulin resistance (Cheng et al., 2004) and interrupts insulin secretion (Dagogo-Jack, 2008), which increases blood glucose levels.

Moreover, having chronic diseases increases symptom burden (Harding, Molloy, Easterbrook, Frame, & Higginson, 2006; Zuniga, Nguyen, & Holstad, 2016) such as loss of energy, mental drowsiness, sleeping problems, and pain (Lee et al., 2009). Symptom burden is defined as "the observations of the patient, the person experiencing the evidence of disease or physical disturbance" (Cleeland, 2007, p.17). The World Health Organization (WHO) advocates that healthcare professionals need to control symptoms in PLWH (World Health Organization, n.d.) because having symptom burdens relates to the poor health outcomes such as poor medicine adherence, decreased patient quality of life, as well as progression of the HIV disease (Gay et al., 2011; Gonzalez et al., 2007; Harding et al., 2012; Holzemer et al., 2001; World Health Organization, n.d.). Thus, it is important to take care about symptom burden care in PLWH+DM.

Due to prolonged life in PLWH, the portion of older adults (OA) in PLWH is growing sharply (Effros et al., 2008), accounting for 17% of PLWH in 2014 (CDC, 2017c). Followed by the previous studies, older adults living with HIV (OALWH) are considered over 50 years old in PLWH (Emlet, 2006; Legarth et al., 2016; Savasta, 2004; Webel et al., 2014). PLWH over the age of 50 have unique barriers to managing their conditions such as age-related comorbid conditions (Emlet & Farkas, 2002). Approximately 30% of OALWH had at least two chronic conditions (Negin et al., 2012). Despite this, there is a lack of studies considering comorbid conditions in OALWH population. Long-term control of both diseases is a key to survival and better quality of use. Many studies demonstrated that retention in care is the most important to HIV management success (Geng et al., 2010) because retention in care enables PLWH to undergo cART, manage of medication toxicity, and prevent HIV treatment failure (Geng et al., 2010). Through this process, we can slow or halt development of disease progression that commonly results in acquired immune deficiency syndrome (AIDS), which is the last stage of HIV (AIDS Info, 2016e). After entering the AIDS stage, mortality rates steeply increase, thereby creating the need to prevent HIV

infections to develop into AIDS, and key to this success is retention in care. Even so, no study thus far has explained the standard measurements of retention in care who have DM with PLWH.

The purpose of this study is to investigate the relationships of retention in care measurements in PLWH+DM by age groups and relationship between symptom burden and retention in care in in PLWH+DM by age groups.

METHODS

Research Design

This study involved a secondary data analysis of the Center for AIDS Research (CFAR) Network of Integrate Clinic Systems (CNICS) database, which includes medical records for PLWH since 1995. This study is a longitudinal retrospective cross-sectional study based on the study by Mugavero, Westfall, et al. (2012), which set the 'gold standard' of measurements in PLWH regardless of comorbid conditions.

Study Setting and Sample

This study involved accessing the CNICS database and collecting data from eight clinical sites: The University of Washington; Case Western Reserve University; The University of California, San Francisco; The University of North Carolina at Chapel Hill; Johns Hopkins University; Fenway Health in Boston; The University of California, San Diego; and The University of Alabama at Birmingham. The CNICS data captured a wide range of information in more than 798 PLWH+DM who were older than 18 years in calendar yeanr2015, and all of the participants were receiving cART from the CNICS clinic sites for at least six months. The CNICS includes demographics (age, gender, race/ethnicity), biomarkers (CD4 cell count, hemoglobin A1c [HbA1c] level), and CNICS clinic visits records. This study used the DM (HbA1c > 6.5 % and/or have DM medications) demographic from the CNICS as a criterion. Health care utilization data consisted of visits and appointment status. This study was considered exempt from the University of Texas at Austin Institutional Review Board because the data from the Center for AIDS Research (CFAR) Network of Integrated Clinic Systems (CNICS) were already de-identified.

Inclusion/Exclusion Criteria

To be considered for inclusion for the study, PLWH+DM samples must have a diagnosis of DM verified by HbA1c > 6.5 % or have DM medications, and have had at least one primary HIV-care appointment at a CNICS clinic site during the 2015 calendar year. This study considered retention in care in only the 2015 calendar year.

Sample Size

To determine the power of our research, the researchers presented the results of the power analyses to justify the sample size using G-Power 3.1.9.2 for Mac (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). In the power analysis for the Spearman's correlation coefficient for power, the total sample size needed is 23 people at an alpha of 0.05, a power of 0.80, and a medium effect size ($\varrho = 0.5$) (Cohen, 1992). Seeing this, the sample size for the current study is sufficient to meet the power requirements. The total sample was 798 PLWH+DM.

Measures of Retention in Care in PLWH+DM

Demographic Measures

Demographic measures included age (dichotomous, 0: > 50 years old, 1: $\leq$ 50 years old), present gender, race/ethnicity, and CD4 cell count (categorical, 0: ≥ 500 cells/μL, 1: 200–499 cells/μL, 2: < 200 cells/μL). For DM diagnosis, we used HbA1c level over > 6.5% and/or having DM medications, which the CNICS defined.

Measures of Retention in Care in PLWH+DM

The measures of retention in care in PLWH+DM were number of missed clinic visits, number of clinic visits attendance (attendance), visit adherence, and visit consistency during the one-year period (2015). Missed visits included no-show visits that were not cancelled or bumped by clinic staff, which refers to people missing clinic appointments without any notice. Missed visits were coded using a count and dichotomous measure (0: visits vs. 1: no-show visits). Attendance was shown as the total counts of participants who actually visited clinics during the 2015 calendar

year (continuous). Visit adherence was calculated as a proportion of appointments kept compared to appointments scheduled (continuous, range: 0–100%). Visit constancy was measured three ways: 4-month visiting constancy, 6-month visiting gap, and the U.S. Health Resources and Services Administration HIV/AIDS Bureau (HRSA HAB) measure outcomes. The 4-month visiting constancy considered the number of patients who had kept visits (categorical, range: 0–3), and the 6-month visiting gap assessed whether patients made visits at least once in no less than 189 days using a dichotomous measure (0: not retained, 1: retained). The HRSA HAB measure determined whether patients made their visits at least 90 days apart using a dichotomous measure during 2015 (0: not retained, 1: retained 90-day gap).

Outcome Variables

There were two outcome variables to measuring retention in care in PLWH+DM: HIV disease control and DM disease control. HIV disease control was measured by CD4 cell count at the last visit. DM disease control was assessed through most recent HbA1c level. A CD4 cell count under 200 cells/μL is considered the last stage of HIV infection, commonly called AIDS and common people have CD4 cell count no more than 500 cells/μL, which indicates sustained good health status of HIV treatments (AIDS Info, 2016b). The HbA1c level reflects three-month glycemic control (Nasir et al., 2010), which signifies DM management to physician and patients (Cagliero, Levina, & Nathan, 1999). Usually, the DM control in PLWH used a HbA1c less than 6.5% (Eckhardt et al., 2012; Tien et al., 2012).

To investigate symptom burden and retention in care in PLWH+DM, we used the HIV Symptom Index (Justice et al., 2001), which consists of 20 items, namely fatigue, fever, dizzy, neuropathy, memory loss, nausea, diarrhea, sadness, anxious, sleep problems, skin problems, coughing, headache, loss appetite, bloating, muscle aches, sex problems, body fat, weight loss, and hair loss. The HIV Symptom Index has 5 response choices—0: I do not have the symptom; 1: I have the symptom, but it does not bother me; 2: I have the symptom, but it bothers me little; 3: I

have the symptom, and it bothers me some; or 4: I have the symptom, and it bothers me a lot (Justice et al., 2001).

Statistical Analyses

Descriptive statistical analyses included demographic characteristics (age, present gender, race/ethnicity, missed visit [count, dichotomous], attendance, visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure, HbA1c level, CD4 cell count) using means, standard deviation (SD), range of scores, frequencies, and percentages.

Spearman's correlation coefficients were used to evaluate the associations among retention in care measurements and health outcomes (CD4 cell count, HbA1c level). Spearman's correlation coefficients were used to test the associations among retention in care measurements (missed visit [count, dichotomous], visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure) by age groups. Logistic regression investigated association between retention in care measurements (missed visit [count, dichotomous], visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure), and HIV infection health status determined by a CD4 cell count of no more than 500 cells/μL by two age groups.

To investigate the association between the symptom burden in PLWH+DM using the HIV symptom index by different age groups and retention in care, researchers conducted logistic regression. To investigate association between retention in care and symptom burden, we used the HRSA HAB measure which was dichotomous variables (0: not retained; 1: retained 90-days gap). To investigate the relationships between retention in care measurements and disease control (CD4 cell count, HbA1c level) in PLWH+DM by age groups, the researchers conducted multi-group path analysis. For path analysis, we considered missed visits (count), visit attendance (count, actual visit clinic times), visit adherence, and 4-month visit constancy for retention in care in PLWH+DM as independent variables and CD4 cell count and HbA1c level as dependent variables. The chi-square statistic, the normed fit index (NFI), the Tucker-Lewis Index (TLI), the comparative fit index (CFI), and root mean square error of approximation (RMSEA) were used to estimate model

fit. All significant statistic levels are within $p < 0.05$. All statistical analyses were conducted using SPSS version 23.0 for PC (IBM Corp, Released 2015) and AMOS version 23.0 for PC (Arbuckle, 2014).

RESULTS

Descriptive Statistics

Study Characteristics in PLWH+DM in All Age Groups

The total number of PLWH+DM in this study was 798. Descriptive statistics are presented in the respective sections on Table 4. The mean age of participants was 55.01years ± 8.961, 77.4% were male, and the most-often reported race or ethnicity was PLWH White-Non-Hispanic (41.1%) followed quite closely by African American-Non-Hispanic (40.3%). PLWH+DM had a mean HbA1c level of 7.565 ± 1.93 (n = 179), and 64.2% had a HbA1c level over 6.5%. Also, 32% had a CD4 cell count of less than 500 cells/μL, and 6.7% of them had less than 200 cells/μL, which is classified as AIDS which is the last stage of HIV. PLWH+DM missed visits (count) mean was 0.29 ± 0.90 during the 12-month period in 2015, and among them, 16.3% had at least more than one missed visit. Their attendance range was 0–26 in 2015, and the mean was 3.07 ± 2.517. Mean of visit adherence was 0.904 ± 0.24, and 5.9% of PLWH+DM visit adherence occurred less than 50% of the time. Among 772, only 29% attended all of their 4-month constancy visits, among 606, 5.9% had a 6-month or greater gap, and 31% were not retained in the HRSA HAB measure (n = 606).

Study Characteristics in OALWH +DM and YALWH+DM

The sample of OALWH+DM was 564 with a mean age of 59.35 years ± 7.22, and YALWH+DM numbered 234, with a mean 44.56 years ± 5.10 (see Table 4). The two groups were statistically similar in missed visits (count, dichotomous), visit adherence, 4-month visit constancy, 6-month gap, CD4 cell count, and HbA1c level ($p > 0.05$). However, there were significant differences between the two groups in gender, race/ethnicity, and attendance ($p <$

0.05). Both OALWH+DM and younger adults living with HIV (YALWH) with DM mostly consisted of male participants (80%, and 71.4%, respectively; $p = 0.01$). The most common race/ethnicity were white–Non-Hispanic in OALWH+DM (45.2%) and African American–Non-Hispanic in YALWH+DM (45.3%) ($p = 0.001$). The attendance range was 0 to 26 in both groups, and there were significant mean differences in attendance (OALWH+DM; 3.05 ± 2.417, YALWH+DM: 3.12 ± 2.747). The mean of visit attendance in OALWH+DM was 3.05 ± 2.417 and 3.12 ± 2.747 in YALWH+DM ($p = 0.01$).

Table 4. Study characteristics in PLWH+DM

Characteristics	All age groups PLWH+DM (N = 798)‡	OALWH+DM (N = 564)‡	YALWH+DM (N=234)‡	Pearson Chi-Square or Fisher Exact‡‡
Age (years) Mean ± SD	55.01 ± 8.96	59.35 ± 7.22	44.56 ± 5.10	
OALWH+DM	564 (70.7%)			
YALWH+DM	234 (29.3%)			
Gender				0.01**
Male	618 (77.4%)	451 (80%)	167 (71.4%)	
Female	180 (22.6%)	113 (20%)	67 (28.6%)	
Race/Ethnicity	n = 794	n = 560		0.001***
White—Non-Hispanic	326 (41.1%)	253 (45.2%)	73 (31.2%)	
White—Hispanic	98 (12.3%)	62 (11.1%)	36 (15.4%)	
African American—Non-Hispanic	320 (40.3%)	214 (38.2%)	106 (45.3%)	
African American—Hispanic	3 (0.4%)	0 (0%)	3 (1.3%)	
Hispanic	18 (2.3%)	12 (2.1%)	6 (2.6%)	
Others	29 (3.7%)	19 (3.4%)	10 (4.3%)	
Missed visits (count)	Range: 0–12	Range: 0–5	Range: 0–12	0.23
Mean ± SD	0.29 ± 0.90	0.24 ± 0.66	0.41 ± 1.30	
Zero	667 (83.6%)	476 (84.4%)	191 (81.6%)	
One	84 (10.5%)	61 (10.8%)	23 (9.8%)	
Two	27 (3.4%)	16 (2.8%)	11 (4.7%)	
≥ Three	20 (2.4%)	11 (2%)	9 (3.7%)	
Missed visits (Dichotomous)				0.35
No missed visits	667 (83.6%)	476 (84.4%)	191 (81.6%)	
Have at least one missed visits	1 (16.4%)	88 (15.6%)	43 (18.4%)	

Table 4. Continued

Characteristics	All age groups PLWH+DM (N = 798)‡	OALWH+DM (N = 564)‡	YALWH+DM (N=234)‡	Pearson Chi-Square or Fisher Exact‡‡
Attendance *Mean ± SD*	Range: 0–26 3.07 ± 2.517	Range: 0–26 3.05 ± 2.417	Range: 0–26 3.12 ± 2.747	0.01**
Visit adherence				0.06
Mean ± SD	0.904 ± 0.24	0.910 ± 0.23	0.890 ± 0.25	
0 – 24%	33 (4.1%)	23 (4.1%)	10 (4.3%)	
25 – 49%	15 (1.8%)	12 (2.1%)	3 (1.3%)	
50 – 74%	62 (7.9%)	34 (6%)	28 (11.6%)	
75 – 99%	47 (5.9%)	37 (6.6%)	10 (4.2%)	
100%	641 (80.3%)	458 (81.2%)	183 (78.2%)	
4-month visit constancy (Intervals with ≥ 1 kept visit)	n = 772	n = 546	n = 226	0.67
Zero	7 (0.9%)	5 (0.9%)	2 (0.9%)	
One	207 (26.8%)	143 (26.2%)	64 (28.3%)	
Two	334 (43.3%)	244 (44.7%)	90 (39.8%)	
Three	224 (29%)	154 (28.2%)	70 (31%)	
6-month gap *(≥189 days between sequential kept visits)*	n = 606	n = 425	n = 181	0.19
No (retained)	570 (94.1%)	396 (93.2%)	174 (96.1%)	
Yes (not retained)	36 (5.9%)	29 (6.8%)	7 (3.9%)	
HRSA HAB measure *(2 kept visits > 90 days apart)*	n = 606	n = 425	n = 181	0.39
Retained	418 (69%)	298 (70.1%)	120 (66.3%)	
Not retained	188 (31%)	127 (29.9%)	61 (33.7%)	

Table 4. Continued

Characteristics	All age groups PLWH+DM (N = 798)‡	OALWH+DM (N = 564)‡	YALWH+DM (N=234)‡	Pearson Chi-Square or Fisher Exact‡‡
HbA1c	n = 179	n = 179	n = 179	0.07
Mean ± SD	7.565 ± 1.93	7.529 ± 1.90	7.69 ± 2.03	
≤ 6.5%	64 (35.8%)	50 (36%)	14 (35%)	
> 6.5%	115 (64.2%)	89 (64%)	26 (65%)	
CD4 cell count	n = 194	n = 151	n = 43	0.61
Mean ± SD	717.84 ± 407.42	696.44 ± 387.06	792.98 ± 469.35	
≤ 500 cells/μL	132 (68%)	102 (67.5%)	30 (69.8%)	
200 – 499 cells/μL	49 (25.3%)	40 (26.5%)	9 (20.9%)	
< 200 cells/μL	13 (6.7%)	9 (6%)	4 (9.3%)	

‡: Indicates the total sample size of the groups, but some variables have different sample sizes as presented on each table.
‡‡: Pearson Chi-Square or Fisher Exact between OALWH+DM, and YALWH+DM
*: Significant level $p < 0.05$
**: Significant level $p < 0.01$
*** : Significant level $p < 0.001$

Retention in Care Measurements

PLWH+DM in All Age Groups

To compare the six measurements of retention in care in PLWH+DM, we conducted the Spearman's correlation coefficients at the significance level $p < 0.05$ (see Table 5). Missed visits (dichotomous) correlated as highly positively with missed visits (count) measurement (0.996) at the significance level of $p < 0.01$. Visit adherence had a high negative correlation with missed visits measurements (count/dichotomous) (–0.854, $p < 0.01$). Despite these findings, 4-month visit constancy and 6-month gap demonstrated that no significant correlation existed between missed visits (count, dichotomous) and visit adherence ($p < 0.05$), and only 4-month visit constancy and 6-month gap had a low negative correlation between them (–0.105, $p < 0.01$). The HRSA HAB measure had lower positive correlations with visit adherence (0.130, $p < 0.01$), and 6-month gap (0.169, $p < 0.01$). Moreover, the other measurement (missed visits [count, dichotomous] had a negative correlation with the HRSA HAB measure (–0.141, –0.140, respectively, $p < 0.01$). On the contrary, the HRSA HAB measure had a high positive correlation with 4-month visit constancy (0.93, $p < 0.05$).

OALWH+DM

By comparison, when we conducted the Spearman's correlation coefficients for all six retention in care measurements for OA resulted in a different correlation pattern, with fewer significant correlations (See Table 6). Missed visits (count) and (dichotomous) variables correlated highly positively (0.997, $p < 0.01$), and those variables had a high negative correlation with visit adherence (–0.854, –0.855, respectively, $p < 0.01$). However, 4-month visit constancy and 6-month gap measurements did not have significant correlations with missed visits (count, dichotomous) and visit adherence. Only 4-month visit constancy and 6-month gap had a low negative correlation between them (–0.126, $p < 0.01$). Differently from the all age group of PLWH+DM, the HRSA HAB measure was not correlated with 4-month visit constancy in

OALWH+DM. Moreover, the other variables (missed visits [count, dichotomous], visit adherence, 6-month gap) and the HRSA HAB measure had low correlations (0.130 to 0.179, $p < 0.01$).

YALWH+DM

YA LWH+DM had a different correlation pattern than the two previous groups (see Table 7). Missed visit (count) and missed visit (dichotomous) had a high positive correlation (0.994, $p < 0.01$). Missed visits (count, dichotomous) and visit adherence had a high negative correlation (–0.852, –0.853, respectively, $p < 0.01$). The HRSA HAB measure had a low positive correlation with 4-month visit constancy (0.182, $p < 0.05$). Except for these variables, the other measurements failed to significantly correlate with each other.

Association between Retention in Care Measures and CD4 cell count

Next, we investigated the relationship between retention in care and CD4 cell count (see Table 8). For OALWH+DM (n = 105), the Hosmer-Lameshow Chi-square was over 0.05, indicating the model fits were appropriate. The only significant relationship between retention in care measurements and CD4 cell count in OALWH+DM was missed visits (count) (EXP(B) = 11.277 95% CI: 1.499-84.843, $p < 0.05$), which means that having more missed visits results in having 11.277 times higher than 500 cells/ μL CD4 cell count. However, YALWH+DM (n = 34), no significant association occurred between retention in care measurements and CD4 cell count at $p < 0.05$ (Hosmer-Lameshow Chi-square $p > 0.05$).

Association with HIV Symptom Burden and Retention in Care

For the whole sample (N = 501), the association between HIV symptom burden and retention in care (HRSA HAB measure) investigated at the significant level $p < 0.05$ (see Tables 9 and 10). There were no significant relationships between HIV symptom burden and retention in care in YALWH+DM (N = 153; $p < 0.05$). Conversely, OWL PLWH+DM (N = 348) had significantly relationships between fatigue, memory loss, and sadness and retention in care ($p < 0.05$). Of OALWH+DM having less fatigue, 0.584 times (95% CI: 0.363-0.938) higher retained,

those with less memory loss had 0.35 times higher retained (95% CI: 0.399-1.011), and those having less sadness had 1.937 times higher retained (95% CI: 1.235-3.038).

Table 5. Spearman's correlation coefficients in PLWH+DM in all age group

	Missed visits (count)	Missed visits (dichotomous)	Visit adherence	4-month visit constancy	6-month gap	HRSA HAB measure
Missed visits (count, range: 0-12)	1					
Missed visits (dichotomous)	0.996**	1				
Visit adherence (continuous, range: 0–1)	–0.854**	–0.854**	1			
4-month visit constancy (categorical, range: 0–3)	0.005	0	0.33	1		
6-month gap (dichotomous)	0.02	0.024	–0.029	–0.105**	1	
HRSA HAB measure (dichotomous)	–0.141**	–0.140**	0.130**	0.93*	0.169**	1

** Significant at $p < 0.01$
* Significant at $p < 0.05$

Table 6. Spearman's correlation coefficients in OALWH+DM

	Missed visits (count)	Missed visits (dichotomous)	Visit adherence	4-month visit constancy	6-month gap	HRSA HAB measure
Missed visits (count, range: 0–5)	1					
Missed visits (dichotomous)	0.997**	1				
Visit adherence (continuous, range:0–1.0)	–0.854**	–0.855**	1			
4-month visit constancy (categorical, range: 0–3)	0.022	0.023	0.11	1		
6-month gap (dichotomous)	–0.009	–0.003	–0.002	–0.126**	1	
HRSA HAB measure (dichotomous)	–0.143**	–0.143**	0.130**	0.05	0.177**	1

** Significant at $p < 0.01$

Table 7. Spearman's correlation coefficients in YALWH+DM

	Missed visits (count)	Missed visits (dichotomous)	Visit adherence	4-month visit constancy	6-month gap	HRSA HAB measure
Missed visits (count, range: 0 – 12)	1					
Missed visits (dichotomous)	0.994**	1				
Visit adherence (continuous, range: 0 – 1.0)	–0.852**	–0.853**	1			
4-month visit constancy (categorical, range: 0–3)	–0.027	–0.050	0.074	1		
6-month gap (dichotomous)	0.11	0.111	–0.123	–0.55	1	
HRSA HAB measure (dichotomous)	–0.133	–0.131	0.125	0.182*	0.143	1

** Significant at $p < 0.01$
* Significant at $p < 0.05$

Table 8. Associations between retention in care measures and CD4 cell count (≤ 500 cells/μL) among PLWH+DM by age groups

Age group	Variables‡	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
								Lower	Upper
OALWH+DM (N = 105)	Missed visits (count)	2.423	1.03	5.537	1	0.019*	11.277	1.499	84.843
	Missed visits (dichotomous)	2.069	1.716	1.454	1	0.228	7.918	0.274	228.713
	Visit adherence	5.582	5.733	0.948	1	0.33	265.714	0.004	20153270.43
	4-month visit constancy	0.685	0.566	1.464	1	0.226	1.983	0.654	6.014
	6-month gap	0.407	0.864	0.222	1	0.638	1.502	0.276	8.173
	HRSA HAB measure	0.082	0.618	0.018	1	0.894	1.086	0.323	3.648
	Constant	-9.479	5.378	3.107	1	0.078	0		
	Total Chi-square (df), p-value: 10.421 (6), $p > 0.05$								
	Hosmer-Lameshow Chi-square (df), p-value: 0.89 (3), $p > 0.05$								
YALWH+DM (N = 34)	Missed visits (count)	10.804	16337.328	0	1	0.999	49219.776	0	.
	Missed visits (dichotomous)	30.158	62616.205	0	1	1	1.25186E+13	0	.
	Visit adherence	4.645	235894.115	0	1	1	104.095	0	.
	4-month visit constancy	0.185	1.645	0.013	1	0.911	1.203	0.048	30.251
	HRSA HAB measure	-0.849	1.465	0.336	1	0.562	0.428	0.024	7.56
	Constant	-35.14	180003.341	0	1	1	0		
	Chi-square (df), p-value: 7.07 (6), $p > 0.05$								
	Hosmer-Lameshow Chi-square (df), p-value: 2.29 (4), $p > 0.05$								

* Significant at $p < 0.05$

‡: Step 1[a]. variables: missed visits (count), missed visits (dichotomous), visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure; Step 1[b]. variables: missed visits (dichotomous), visit adherence, 4-month visit constancy, HRSA HAB measure

Table 9. Association between HIV symptom burden and retention in care using logistic regression[‡] in OALWH+DM (N = 348)

HIV Symptom Index	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Fatigue	-0.538	0.242	4.95	1	0.026*	0.584	0.363	0.938
Memory loss	-0.454	0.237	3.67	1	0.055*	0.635	0.399	1.011
Sadness	0.661	0.23	8.284	1	0.004**	1.937	1.235	3.038
Constant	-2.352	0.301	60.891	1	0	0.095		
Chi-square (df), p-value: 50.62 (21), $p < 0.01$								
Hosmer-Lameshow Chi-square (df), p-value: 0.000 (8), $p > 0.05$								

[‡]: Used backward stepwise
** Significant at $p < 0.01$
* Significant at $p < 0.05$

Table 10. Association between HIV symptom burden and retention in care using logistic regression[‡] in YALWH+DM (N = 153)

HIV Symptom Index	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Fatigue	21.471	2068.809	0	1	0.992	2112528447	.	.
Fever	-27.257	14217.655	0	1	0.998	0	.	.
Dizzy	-14.589	4718.65	0	1	0.998	0	.	.
Neuropathy	-22.525	3371.868	0	1	0.995	0	.	.
Memory loss	-34.677	8869.15	0	1	0.997	0	.	.
Nausea	17.1	4117.812	0	1	0.997	26685542.05	.	.
Diarrhea	-19.655	5441.829	0	1	0.997	0	.	.
Sadness	-35.414	14638.758	0	1	0.998	0	.	.
Anxious	32.051	13009.45	0	1	0.998	8.31266E+13	.	.
Sleep problem	22.293	2720.998	0	1	0.993	4807728150	.	.
Skin problem	-68.479	4640.308	0	1	0.988	0	.	.
Cough	12.576	3256.575	0	1	0.997	289590.116	.	.
Headache	15.313	6777.269	0	1	0.998	4468795.852	.	.
Loss appetite	-30.357	6736.416	0	1	0.996	0	.	.
Bloating	-13.457	2912.79	0	1	0.996	0	.	.
Muscle aches	-17.564	2583.466	0	1	0.995	0	.	.
Sex problem	-51.422	6370.456	0	1	0.994	0	.	.
Bodyfat	31.55	1967.198	0	1	0.987	5.03675E+13	.	.
Weight loss	59.982	3757.769	0	1	0.987	1.12139E+26	0	.
Hair loss	-7.246	4911.736	0	1	0.999	0.001	0	.
Constant	-98.509	3853.126	0.001	1	0.98	0		
Chi-square (df), *p*-value: 50.62 (21), $p < 0.01$								
Hosmer-Lameshow Chi-square (df), *p*-value: 0.000 (8), $p < 1.0$								

[‡]: Used backward stepwise

Retention in Care and Disease Control Paths

We divided the full sample into age groups (OALWH+DM, YALWH+DM) for path analysis. For the analysis path, we used retention in care measurements (missed visit [count], attendance, visit adherence, 4-month visit constancy, and disease control [CD4 cell count, HbA1c leve]) at the significant level $p < 0.05$. The total PLWH+DM study sample was (N = 772, OALWH+DM n = 546; YALWH+DM, n = 226). Each path diagram represents path coefficients and squared multiple correlations in Figures 5, 6 and Table 12. Our hypothesized path model is presented in Figure 4, and it applies to the different age groups in PLWH+DM.

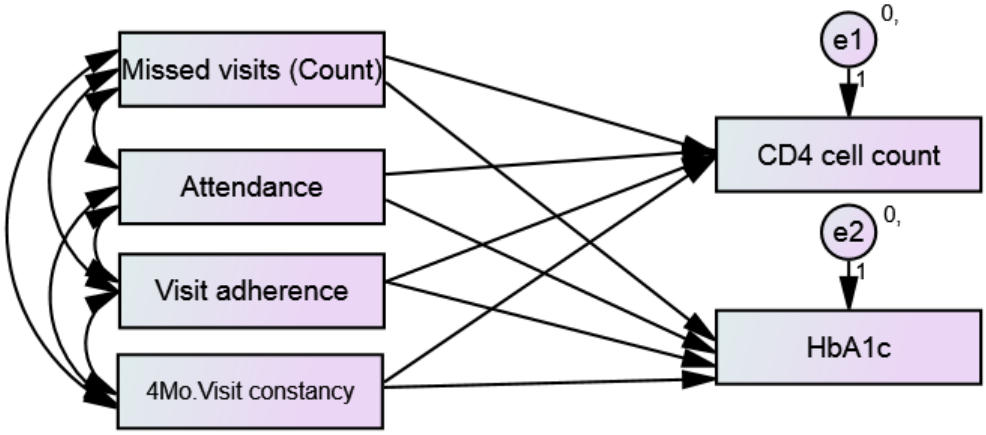
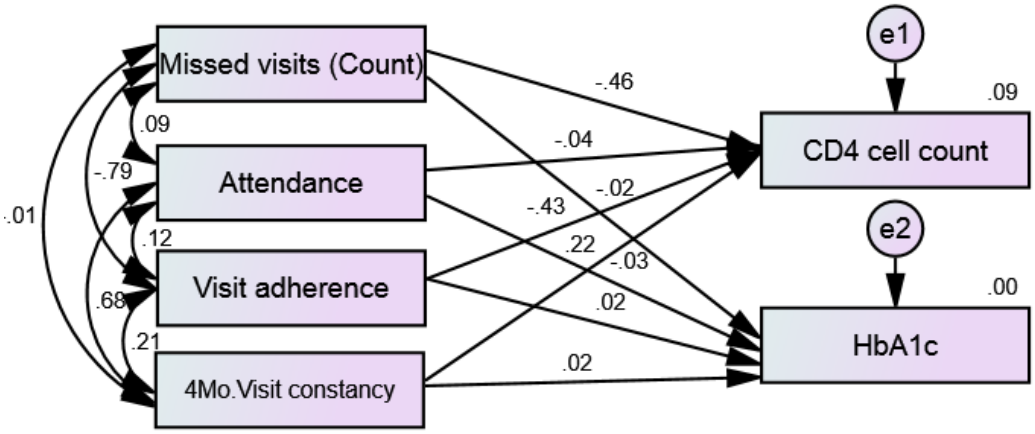


Figure 4. Hypothesized path model in PLWH+DM.

Retention in Care and Disease Control in OALWH+DM

We conducted path analysis with just OALWH+DM and found that three of the hypothesized paths were significant (see Figure 5), and the model fit was $\chi 2 = 0.066$, df = 2, P = 0.968, NFI = 1.0, RMSEA = 0.00, CFI = 1.00, TLI = 1.03 (N = 546) (see Table 11). The model fit was quite good. Thus, we did not need to perform re-modeling. Figure 5 and Table 12 indicate the hypothesized paths and coefficients in OALWH+DM. For this model, the significant paths consisted of missed visits (count), visit adherence and 4-month visit constancy related significantly with CD4 cell count at significant level $p < 0.05$. However, between HbA1c level and missed visits

(count), attendance, visit adherence and 4-month visit constancy ($p < 0.05$) had no significantly relationships. Moreover, missed visits (count) and visit adherence had a significant relationship each other, and visit adherence and 4-month visit constancy had a significant relationship each other ($p < 0.05$).



Chi-square (df) = 0.066(2)
Probability (P) = 0.968
Likelihood ratio (Chi-square/df) = 0.033
NFI = 1.00
RMSEA = 0.00
CFI = 1.00
TLI = 1.03

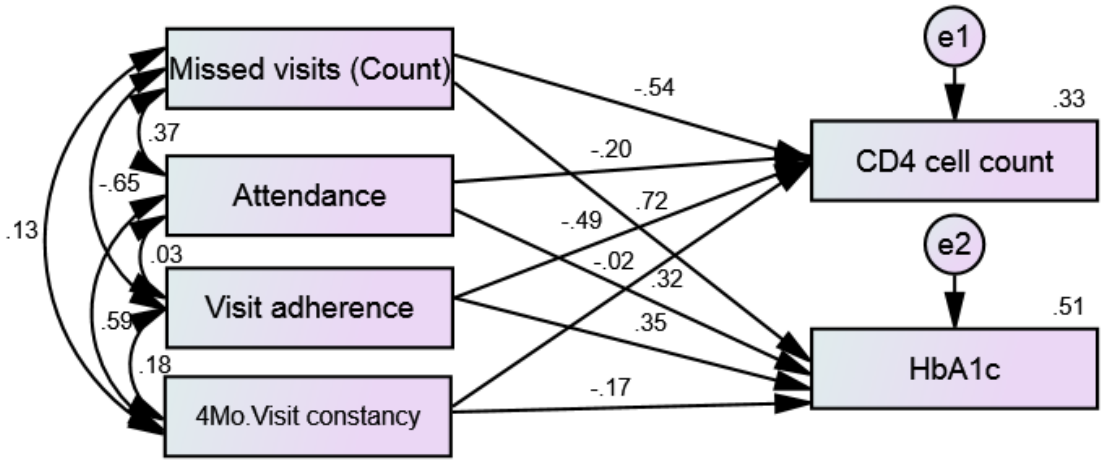
Notes. CFI, comparative fit index; NFI. normed fit index; RMSEA, root mean square error of approximation; TLI, Tucker-Lewis Index

Figure 5. Hypothesized model with path coefficients in OALWH+DM

Retention in Care and Disease Control Paths in YALWH+DM

Finally, we conducted the path analysis with the YALWH+DM, and some differences persisted in this group when compared to OA with LWH+DM (see Figure 6). The hypothesized path in the group of YALWH+DM was ($\chi 2 = 0.066, df = 2, P = 0.968, NFI = 1.0, RMSEA = 0.00,$

CFI = 1.00, TLI = 1.03 [N = 226]) (see Figure 6 and Table 11). Model fit was satisfied, so we did not need re-modeling. Path analysis indicated that missed visits (count), and visit adherence had significant relationships with CD4 cell count ($p < 0.05$). In addition, missed visits (count), attendance and visit adherence had significant relationships with HbA1c level in YALWH+DM ($p < 0.05$). Moreover, missed visits (count) had significant relationships with visit attendance and visit adherence ($p < 0.05$).



Chi-square (df) = 0.066(2)
Probability (P) = 0.968
Likelihood ratio (Chi-square/df) = 0.033
NFI = 1.00
RMSEA = 0.00
CFI = 1.00
TLI = 1.03

Notes. CFI, comparative fit index; NFI. normed fit index; RMSEA, root mean square error of approximation; TLI, Tucker-Lewis Index

Figure 6. Hypothesized model with path coefficients in YALWH+DM

Table 11. Model fit comparisons by age group‡

Age group	χ2	df	P	NFI	RMSEA	CFI	TLI
OALWH+DM	0.066	2	0.968	1.0	0.00	1.00	1.03
YALWH+DM	0.066	2	0.968	1.0	0.00	1.00	1.03

‡: All the models are significant at $p < 0.05$

Notes. χ^2. chi-square; CFI, comparative fit index; df: degree of freedome; P: probability, NFI: normed fit index; TLI, Tucker-Lewis Index; RMSEA; root mean square error of approximation

Table 12. Standardized path coefficients by age groups

Model	Path	Path coefficient	*p* value
OALWH+DM	*Standardized effects on CD4 cell count*		
	Missed visits (count)	–0.46***	0.001
	Attendance	–0.04	0.73
	Visit adherence	–0.43**	0.002
	4-month visit constancy	0.22*	0.040
	Standardized effects on HbA1c level		
	Missed visits (count)	–0.02	0.89
	Attendance	–0.03	0.78
	Visit adherence	0.02	0.90
	4-month visit constancy	0.024	0.84
YALWH+DM	*Standardized effects on CD4 cell count*		
	Missed visits (count)	–0.54**	0.001
	Attendance	–0.20	0.26
	Visit adherence	–0.50**	0.01
	4-month visit constancy	–0.02	0.91
	Standardized effects on HbA1c level		
	Missed visits (count)	0.72***	0.001
	Attendance	0.32*	0.04
	Visit adherence	0.35*	0.03
	4-month visit constancy	–0.17	0.23

* Significant at $p < 0.05$
** Significant at $p < 0.01$
*** Significant at $p < 0.001$

DISCUSSION

Our study first examined differences in retention in care for PLWH of two age groups. OALWH+DM had significantly lower visit attendance than YALWH+DM ($p = 0.01$). This result could possibly be due to the lack of accessibility to the hospitals for OALWH+DM because OA are more vulnerable to lacking social supports, including living alone and lacking health insurance, than YA (Emlet & Farkas, 2002). Seeing this, these vulnerable factors could negatively affect some OALWH in that they might not go to the clinic.

Second, our study assessed the usefulness of six retention in care measurements by age groups. Spearman's correlation coefficients analysis revealed the correlations among retention in care measurements in PLWH+DM differs by age group. The 4-month visit constancy was not correlate with the other retention in care measurements for all age groups. This could be due to the fact that 4-month visit constancy was considered over the 12 months and divided by the shorter term (every 4 months) unlike the other measurements, so it is possible that PLWH+DM could not be retained in such a short-term period. But with the other retention in care measurements, at least either one correlated in each age group. In a previous study by Mugavero, Westfall, et al. (2012), all the retention in care measurements correlated significantly in PLWH, but that study does not consider comorbid conditions. Nevertheless, our study considered comorbid conditions in PLWH. Considering this, 4-month visit constancy might not be an appropriate measurement to PLWH with comorbid conditions.

Third, logistic regression to investigate in association between retention in measurements and disease progression marker (CD4 cell count in three groups), only the missed visits (count) variable in OALWH+DM significantly predicted CD4 cell count, the other measurements were not significantly associated with CD4 cell count. These findings do not agree with previous research. One of the major HIV disease progression marker, VL, according to Mugavero,

Westfall, et al. (2012), whose study included PLWH, regardless of comorbid conditions, all the retention in measurements and VL suppression associated significantly, regardless of comorbid conditions. The reason for the difference from the previous study, it remains possible that patients not well-retained into care develop a comorbid condition.

Fourth, this study examined the multi-group path analysis that affected CD4 cell count and HbA1c levels in PLWH+DM, as divided into two age groups. With these results, we can determine that the missed visits affected the CD4 cell count regardless of age and that retention in care is important to HIV disease control (CD4 cell count) ($p < 0.05$). Most of retention in care measurements were significantly correlated to HbA1c level for YALWH+DM, however it was not significant in OALWH+DM ($p < 0.05$). However, these results were partially consistent with Zuniga et al., (2016) who found that OA have better control of DM and HIV than YA. However, one of the main areas of DM control in PLWH, retention in care in OA, did not significantly correlate with HbA1c level. This result could possibly be due to the fact that DM is more self-management disease, requires daily glucose monitoring, dietary management (Vijan, Sussman, & Yudkin, 2014), medication adherence (Patel, Chang, Shenolikar, & Balkrishnan, 2010), and OALWH+DM proved more willing to manage effectively the disease than YALWH+DM (Patel et al., 2010). It could thus be possible that OALWH+DM did not rely on just retention in care.

Finally, this study investigated the association between symptom burden using the HIV symptom index and retention in care in PLWH+DM. The OALWH+DM group sample was 348. Among a total 20 items in symptom burden, three symptoms (fatigue, memory loss, sadness) were associated significantly with retention in care (HRSA HAB measure). Nonetheless, no significant association occurred between symptom burden and retention in care in YALWH+DM

at the significant level of 0.05. Because of this, healthcare professionals need to focus more on OALWH+DM than YALWH+DM retention in care as a key to successful management in PLWH (Geng et al., 2010), and having more symptom burden affected retention in care.

LIMITATIONS

This study had several limitations. It consisted of only samples who visited the eight clinics in the CNICS network and also had missing variables. The study results might thus not be generalized to other populations. Also, we do not consider who died during 2015 calendar year, so the results could be biased. But the samples were drawn from eight clinics across the United States, and the sample was large, so our study has representative results. In addition, missing data for CD4 cell count and HbA1c level caused a statistical analysis bias. Prospective studies are necessary to provide better samples regarding CD4 cell count and HbA1c level trajectories in PLWH+DM.

CONCLUSION

We conducted a comparison analysis of retention in care in PLWH+DM divided by two age groups at a large national cohort study over one calendar year. The CD4 cell count affected retention in care measurements regardless of age groups. Nonetheless, HbA1c level was significantly affected by YALWH+DM group. The symptom burden negatively affected the retention in care in OALWH+DM. This is the first study considered by PLWH+DM depending on age groups. Even though our study contained a small number of CD4 cell count and HbA1c level data, these results could be a milestone to research on PLWH+DM in the future.

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Chapter Four: Comparing 10-year Survival Rates in Comorbid Conditions in HIV-infected People Treated with Combined Antiretroviral Therapy (2006—2015)

ABSTRACT

Background/Objectives: Diabetes (DM) is the second most common comorbid condition in persons living with human immunodeficiency virus (HIV) (PLWH). Also, chronic kidney disease (CKD) is highly related to the mortality rate. DM is one of the most major risk factors in CKD. The purpose of this study is to investigate the CKD occurrence rates in PLWH and PLWH+DM, and to calculate the survival rates in each group (PLWH, PLWH+DM, PLWH+DM+CKD) as well as age at initial clinic visit (≤ 30, 31-50, > 50 years old).

Methods: This study is a secondary data analysis using the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS), which included HIV-infected people. This study is a retrospective longitudinal comparison study in 2006 to 2015 years' period. We divided the sample into three disease groups (PLWH, PLWH+DM, PLWH+DM+CKD) and age at initial clinic visit by using the descriptive statistics. Then we compared survival analysis for the three disease groups and at age at initial clinic visit using Kalan-Meier analysis and Cox regression.

Results: Among a total of 10,063 HIV-infected participants, 8,266 people had HIV-infection only without any comorbid conditions, 1,720 had PLWH+DM without CKD, and 57 people had PLWH+DM+CKD. No participants had CKD only in PLWH. In PLWH-only, the mortality rate was only 3.6%, a rate almost three times higher (12.0%) in PLWH+DM than in PLWH-only, and a PLWH+DM+CKD mortality rate occurred at three times higher (36.8%) than PLWH+DM. The overall survival time mean was 19.689 years (95% CI: 19.572-19.806). However, an increased age at initial clinic visit resulted in reduced survival time.

Conclusion: CKD always accompanies DM in PLWH. The survival time increased for those who have only HIV infection as opposed to those who have at least one comorbid conditions. This study indicated that mortality rates increased by comorbid conditions. This study will contribute to guide in survival rates in PLWH with comorbid conditions.

Key words: ART, chronic kidney disease, comorbid conditions, diabetes, HIV, mortality, survival rates

INTRODUCTION

More than one million Americans have Human Immunodeficiency Virus (HIV) (CDC, 2017b). Currently, the mortality rates in those with PLWH in the United States was 4.7 per 100,000 population in 2014 (CDC, 2016). With the significantly development of combined antiretroviral therapy (cART) since the mid of 1990s (Arts et al., 2012), persons living with HIV (PLWH) are approaching the life expectancy of the general population (Lewden et al., 2012; Weber et al., 2013). The non-acquired immunodeficiency syndrome (AIDS)-related mortality rates has increased more than in previous years (Weber et al., 2013).

Approximately 60% of PLWH over 50 years old have at least one comorbid condition (Rolls et al., 2014). Diabetes (DM) is the second-most-common comorbid condition in PLWH (Brown et al., 2005; Butt et al., 2009; Medapalli et al., 2012). The reason for this is that HIV-infection causes disease inflammation through the secretion of pro-inflammatory cytokines, which affected damage CD4 cell count (Appay & Sauce, 2008; Decrion, Dichamp, Varin, & Herbein, 2005) and cARTs increase DM (Smith et al., 2014).

PLWH had three times higher chance to have chronic kidney disease (CKD) than the general population (Bonjoch et al., 2014; Ibrahim et al., 2012; Islam et al., 2012; Schwartz et al., 2005). DM is one of the major risk factors of CKD in PLWH (Estrella & Fine, 2010). DM increases systematic inflammation (Hadigan et al., 2001) with increased insulin resistance (Hotamisligil et al., 1996) to destructed nephrons, and/or functional units of the kidney (Naftalin et al., 2011). Forty-five percent of population of CKD progress to end-stage renal disease (ESRD) (Gilmore, 2006; Whaley-Connell et al., 2009), which is irreversible kidney damage (Bickel et al., 2013). People with ESRD requires dialysis, which highly correlates with mortality rates in PLWH (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004). Among PLWH+CKD patients, at the

ESRD stage, only 33% survive after five years with dialysis (Soleymanian et al., 2006) as opposed to 35% in general population after five years with dialysis (Collins et al., 2014). Thus, regardless of the reduction of the mortality rates in PLWH, it remains important to investigate the survival rates in comorbid conditions in PLWH. Nevertheless, no study exists that relates to the comorbidities of CKD and HIV.

This study had two purposes. First, it sought to investigate the CKD occurrence rates in PLWH, and PLWH+DM in 10-year clinical periods. Second, it sought to assess the survival rates in each group (PLWH, PLWH+DM, PLWH+DM+CKD).

METHODS

Study Setting and Participants

We conducted a retrospective chart review of a longitudinal comparison study using multisite national HIV cohort data from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS). The samples were over 18 years old and receiving cART for over six months, and visited at least one of the eight CNICS clinics located at Case Western Reserve University, University of Alabama at Birmingham, University of California San Francisco, the University of Washington, the University of California San Diego, Fenway Health/Harvard University, University of North Carolina Chapel Hill, and Johns Hopkins University. For this study, we extracted from the medical records in CNICS in 2006—2015 of people who visited at least one time during the study period. This study was exempted from by the Institutional Review Board (IRB) at the University of Texas at Austin.

Disease verification and Mortality ascertainment

Diagnosis of DM was defined as people who have a HbA1c level over 6.5% and/or who are taking DM medications. Diagnosis of PLWH+DM+CKD was defined using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation, which measures kidney functions using the creatinine level (Stevens et al., 2009); greater than 60mL/min/1.73m^2 to be considered CKD.

To ascertainment mortality, mortality rates data were obtained from medical record review from CNICS which includes mortality certification from state vital records and the National Death Index (NDI+). We examined survival rates in each group.

Statistical analysis

This study was tested as a conceptual model which was presented in Figure 2. Descriptive statistics were conducted including means, frequencies, standard deviation (SD), and percentage. Before conducting the analysis, authors assessed the accuracy of the data and excluded missing data. To examine the study characteristics, descriptive statistics were used. It included two age groups ($\leq$ 50 years old, > 50 years old), present sex, race/ethnicity (White, White-Hispanic, African-American, African-American Hispanic, Hispanics, and Others), HbA1c level, and CD4 cell count in PLWH, PLWH+DM, and PLWH+DM+CKD. To examine difference in CKD occurrence, the researcher used the dichotomous variable (0: have CKD, 1: do not have CKD) among PLWH, PLWH+DM, and PLWH+DM+CKD.

To examine survival rates of each group (PLWH, PLWH+DM, PLWH+DM+CKD) and divide by age at patients' initial clinic visits, we used the Kaplan-Meier analysis. Survival time was based on the number of deaths per 100 person-years of follow-up time. Factors included type of disease (categorized as PLWH-only, PLWH+DM, PLWH+DM+CKD), age, race/ethnicity, present sex, CD4 cell count, HbA1c level, age at initial clinic visit, and age groups were divided by two groups ($\leq$ 50 years old, > 50 years old) because comorbid conditions frequently occurred in older adults; PLWH older adults is defined over 50 years old (Emlet, 2006; Legarth et al., 2016; Savasta, 2004; Webel et al., 2014). The mortality rates across groups were compared using the log-rank test at significant level $p < 0.01$ for this study. Moreover, we assessed the relationships between variables (two age groups, present sex, race/ethnicity, HbA1c, CD4 cell count, age at initial clinic visit, and disease groups) and survival rates, using Cox regression. We adjusted confounding factors, which included present sex, race/ethnicity, HbA1c level, CD4 cell count, age at initial clinic visit, and disease groups (PLWH, PLWH+DM, PLWH+DM+CKD) using a

backward-stepwise approach. All analyses were performed at 0.01 significant levels using the Statistical Package for the Social Science (SPSS) for PC version 23.0 (IBM Corp, Released 2015).

RESULTS

Study characteristics

Among a total of 10,063 HIV-infected persons enrolled in the CNICS during the 2006 through 2015, 8,266 people had HIV-infection without DM or CKD (see Table 13), 1,720 were PLWH+DM, and 57 people were PLWH+DM+CKD. Among group of PLWH, 69.8% were no more than 50 years old, 84.7% were male, and 51.3% were White. In addition, PLWH-only, 36.7% had no more than 500 cells/μL in CD4 cell count (n = 946). In addition, a 3.6% mortality rate occurred among PLWH, and 34.6% made an initial clinic visit in their 30s.

Of PLWH+DM (N = 1,720), 74.7% were male, 74.9% were over 50 years old, and most of them were African American (48.9%). The dominant age at initial clinic visit was the 40s (38.3%). The baseline HbA1c level revealed that 54.5% were over the 6.5% level (n = 288), and 42.2% of the baseline CD4 cell counts were no more than 500 cells/μL. Twelve percent of PLWH+DM group died between 2006 and 2015.

Of PLWH+DM+CKD (N = 57), 68.4% were male, 68.4% of people were over 50 years old, and most of them were African American (73.7%). The age at initial clinic visit most frequently occurred for people in their 40s (36.8%) and 50s (28.1%). Almost 37% died from 2006 through 2015.

Following these descriptive statistics, we can recognize that the occurrence of comorbid conditions (DM, CKD) in this research increased by age; PLWH-only mostly consisted of those who were no more than 50 years old, but the other two groups' (PLWH+DM, PLWH+DM+CKD) population mostly consisted of patients over 50 years old. Additionally, this study indicated that the mortality rates increased by comorbid conditions; PLWH-only had a mortality rate of only 3.6% from 2006 through 2015, but if patients had DM with PLWH, the mortality rate was almost

three times higher (12.0%) than PLWH-only, and PLWH+DM+CKD mortality rate was nearly three times higher (36.8%) than PLWH+DM ($p = 0.000$).

Table 13. Study characteristics by disease groups (PLWH, PLWH+DM, PLWH+DM+CKD)

Study Characteristics		All groups‡ N = 10,063		PLWH-only‡ N = 8,266		PLWH+DM‡ N = 1,720		PLWH+DM+CKD‡ N = 57		Pearson Chi-Square or Fisher's Exact Test
		n	%	n	%	n	%	n	%	
Gender	Male	8345	82.9	7022	84.7	1284	74.7	39	68.4	0.56
	Female	1717	17.1	1263	15.2	436	25.3	18	31.6	
	Intersection	1	0	1	0	0	0	0	0	
Age group	> 50 years old	3842	38.2	2504	30.2	1288	74.9	39	68.4	
	≤ 50 years old	6221	61.8	5782	69.8	432	25.1	18	31.6	
Survival	Live	9536	94.8	7987	96.4	1513	88.0	36	63.2	0.000*
	Death	527	5.2	299	3.6	207	12.0	21	36.8	
Race/ Ethnicity	White	4832	48.5	4204	51.3	616	36.0	12	21.1	0.000*
	White-Hispanic	778	7.8	640	7.8	136	7.9	2	3.5	
	African American	3151	31.6	2271	27.7	838	48.9	42	73.7	
	African American-Hispanic	28	0.3	24	0.3	4	0.2	0	0	
	Others	860	8.6	771	9.4	89	5.2	0	0	
	Hispanic	310	3.1	280	3.4	29	1.7	1	1.8	
	Total n	9,959		8,266		1,712				
Age at initial clinic visit	10s	115	1.1	113	1.4	2	0.1	0	0	0.000*
	20s	2385	23.7	2301	27.8	82	4.8	2	3.5	
	30s	3278	32.6	2866	34.6	400	23.3	12	21.1	
	40s	2832	28.1	2153	26.0	658	38.3	21	36.8	

Table 13. Continued

Study Characteristics		All groups‡ N = 10,063		PLWH-only‡ N = 8,266		PLWH+DM‡ N = 1,720		PLWH+DM+CKD‡ N = 57		Pearson Chi-Square or Fisher's Exact Test
		n	%	n	%	n	%	n	%	
Age at initial clinic visit	50s	1212	12.0	742	9.0	454	26.4	16	28.1	0.000*
	60s	216	2.1	104	1.3	108	6.3	4	7.0	
	70s	24	0.2	7	0.1	15	0.9	2	3.5	
	80s	1	0	0	0	1	0.1	0	0	
HbA1c level	> 6.5 %					157	54.5			0.06
	≤ 6.5 %					131	45.5			
	Total n	10,063		8,266		288				
CD4 cell count	> 500 cells/μL	770	62.0	599	63.3	171	57.8			0.33
	200-499 cells/μL	347	27.9	256	27.1	91	30.7			
	≤ 200 cells/μL	125	10.1	91	9.6	34	11.5			
	Total n	1,242		946		296				

‡: Indicates the total sample size of the groups, but some variables have different sample sizes as presented on each table.

*: Significant level at $p < 0.001$

Survival analysis

Of the 10,030 samples, 8253 were PLWH-only, 1,720 were PLWH+DM, and 57 were PLWH+DM+CKD. Each group's occurrence of mortality was 266 in PLWH, 207 in PLWH+DM, and 21 in PLWH+DM+CKD; overall, 494 people died in our study period (see Table 14). The mean of PLWH survival time was 20.135 years per 100 person-years (95% confidence interval [CI]), 20.025-20.246), PLWH+DM survival time was 18.691 years (95% CI, 18.404-18.979), and PLWH+DM+CKD survival time was 15.433 (95% CI, 13.572-17.294) ($p < 0.01$). The overall mean survival time was 19.689 (95% CI, 19.572-19.806). The survival rates for each group are shown in Table 15, and Figure 7.

Table 16 shows the mortality in age at initial clinic visit according to different disease groups. Of PLWH-only, most (n = 5,265) people were no more than 30 years old at initial clinic visit, and the group with the highest number of mortality was no more than 30 years old. But the other two groups (PLWH+DM, PLWH+DM+CKD) showed that most people died when over 30 years old, and they were over 30 years old at initial clinic visit.

Survival time refers to age at initial clinic visit by disease groups that indicates that when following age at initial clinic visit was older, the survival time was reduced regardless of disease groups (see Table 17). In PLWH, age at initial clinic visit occurred on those no more than 30 years, and we can thus assume that they can live around 20.451 years (CI: 20.341-20.56), but if age at initial clinic visit at over 50 years old, they might live 17.935 years (CI: 17.356-18.515). In PLWH+DM, if the age at initial clinic visit happened at no more than 30 years old, they might live 19.768 years (CI: 19.404-20.132) but, if they went made an initial clinic visit at over 50 years old, the survival time was decreased (17.129 years, CI: 16.386-17.872). Of PLWH+DM+CKD, which has more than two comorbid conditions, if the age at initial clinic visit was at no more than 30 years old, they can live around 18.271 years (CI: 16.046-20.496), but if the age at initial clinic visit at over 50 years old, the survival time was only 12.53 years (CI: 9.639-15.421). Further, the results demonstrated that if people have comorbid conditions in PLWH, their survival time is reduced;

the longest survival time was PLWH-only and PLWH+DM, and PLWH+DM+CKD. Figures 8 through 10 indicate that survival time means by age at initial clinic visit by three different disease groups (≤ 30, 31-50, > 50 years old).

To calculate the risk factors associated with the mortality rates, we conducted Cox regression analysis. We controlled race/ethnicity, present sex, two age groups (≤ 50 years old, > 50 years old), baseline CD4 cell count, baseline HbA1c level, age at initial clinic visit, and disease groups (PLWH, PLWH+DM, PLWH+DM+CKD), which might influence to the survival rates. Only age at initial clinic visit and disease groups were risk factors to the survival rates at the significant level of $p < 0.05$. The group of patients with age at initial clinic visit from 31 to 50 years had a mortality rate 2.203 times higher than those with an age at initial clinic visit of no more than 30 years old ($p < 0.01$, CI: 1.766-2.747) (see Table 18). The group with age at initial clinic visit of over 50 years had a 4.275 times higher mortality rate than the group whose age at initial clinic visit was no more than 50 years old at the significant level $p < 0.01$ (CI: 3.366-5.428). Between disease groups, PLWH+DM group had a 1.787 times higher mortality rate than the PLWH-only ($p < 0.01$, CI: 1.47-2.172), and PLWH+DM+CKD had a 4.739 times higher mortality rate than the PLWH-only ($p < 0.01$, CI: 3.016-7.446).

Table 14. Occurrence of mortality in each group

			Censored	
Dx categories	Total N	N of deaths	N	Percent
PLWH-only	8,253	266	7,987	96.80%
PLWH+DM	1,720	207	1,513	88.00%
PLWH+DM+CKD	57	21	36	63.20%
Overall	10,030	494	9,536	95.10%

Notes. censored; persons still survive at that point of the study, Dx; diagnosis

Table 15. Survival time means according to disease categories

Dx categories	Mean		95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound
PLWH-only	20.135	0.056	20.025	20.246
PLWH+DM	18.691	0.147	18.404	18.979
PLWH+DM+CKD	15.433	0.949	13.572	17.294
Overall	19.689	0.06	19.572	19.806

Note. Dx; diagnosis

Table 16. Distribution of age at initial clinic visit and occurrence of mortality

Age at initial clinic visit	Dx categories	Total N	N of deaths	Censored	
				N	Percent
≤ 30	PLWH-only	5,265	108	5,157	97.90%
	PLWH+DM	484	40	444	91.70%
	PLWH+DM+CKD	14	4	10	71.40%
	Overall	5,763	152	5,611	97.40%
31-50	PLWH-only	2,145	97	2,048	95.50%
	PLWH+DM	658	77	581	88.30%
	PLWH+DM+CKD	21	9	12	57.10%
	Overall	2,824	183	2,641	93.50%
> 50	PLWH-only	843	61	782	92.80%
	PLWH+DM	578	90	488	84.40%
	PLWH+DM+CKD	22	8	14	63.60%
	Overall	1,443	159	1,284	89.00%
Overall	Overall	10,030	494	9,536	95.10%

Notes. censored; persons still survive at that point of the study, Dx; diagnosis

Table 17. Survival time means by age at initial clinic visit by disease categories

Age at initial clinic visit	Dx categories	Mean		95% Confidence Interval	
		Estimate	Std. Error	Lower Bound	Upper Bound
≤ 30	PLWH-only	20.451	0.056	20.341	20.56
	PLWH+DM	19.768	0.186	19.404	20.132
	PLWH+DM+CKD	18.271	1.135	16.046	20.496
	Overall	20.292	0.059	20.177	20.407
31-50	PLWH-only	19.728	0.143	19.448	20.008
	PLWH+DM	18.819	0.226	18.375	19.263
	PLWH+DM+CKD	14.744	1.357	12.084	17.404
	Overall	19.249	0.129	18.996	19.503
> 50	PLWH-only	17.935	0.296	17.356	18.515
	PLWH+DM	17.129	0.379	16.386	17.872
	PLWH+DM+CKD	12.53	1.475	9.639	15.421
	Overall	17.734	0.266	17.212	18.256
Overall	Overall	19.689	0.06	19.572	19.806

Notes. Dx; diagnosis

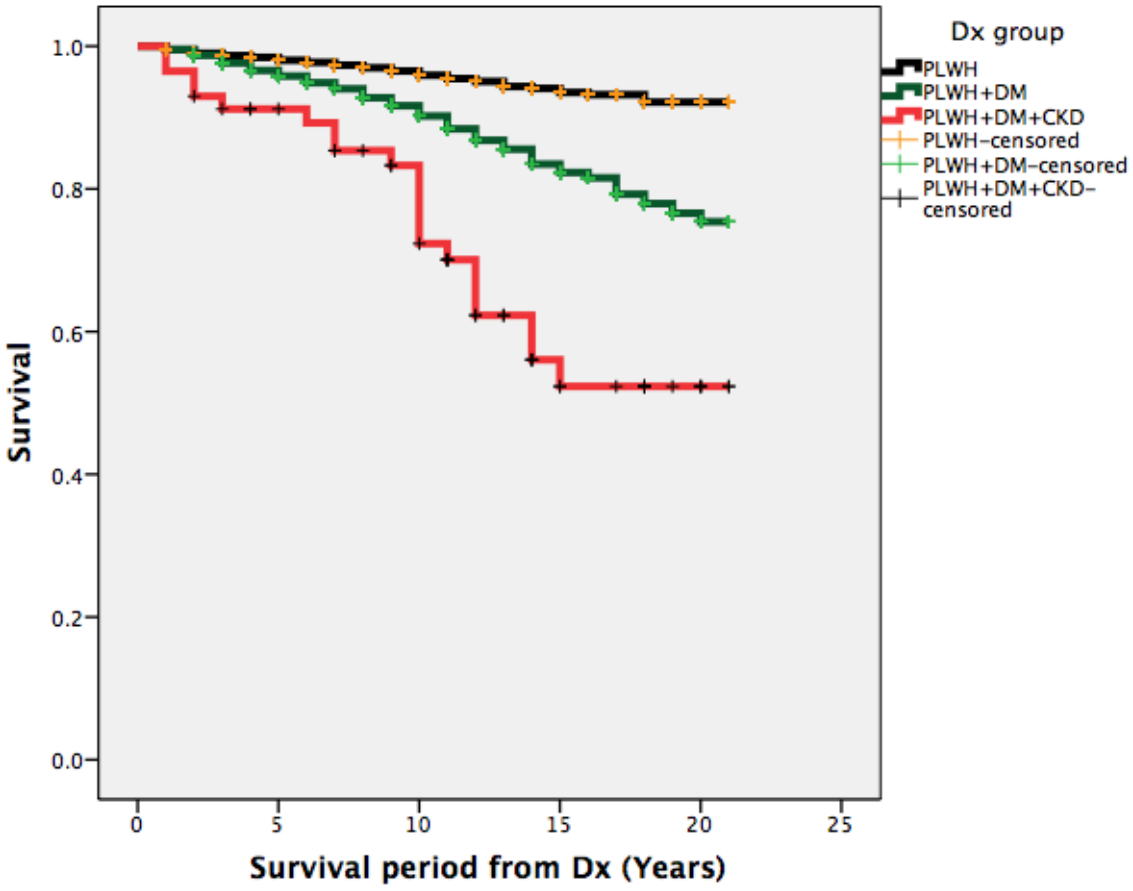

Figure 7. Kaplan-Meier survival curves for all-cause mortality among patients classified by all age disease group (PLWH, PLWH+DM, PLWH+DM+CKD), log rank $p < 0.01$

Notes. censored; persons still survive at that point of the study, Dx; diagnosis

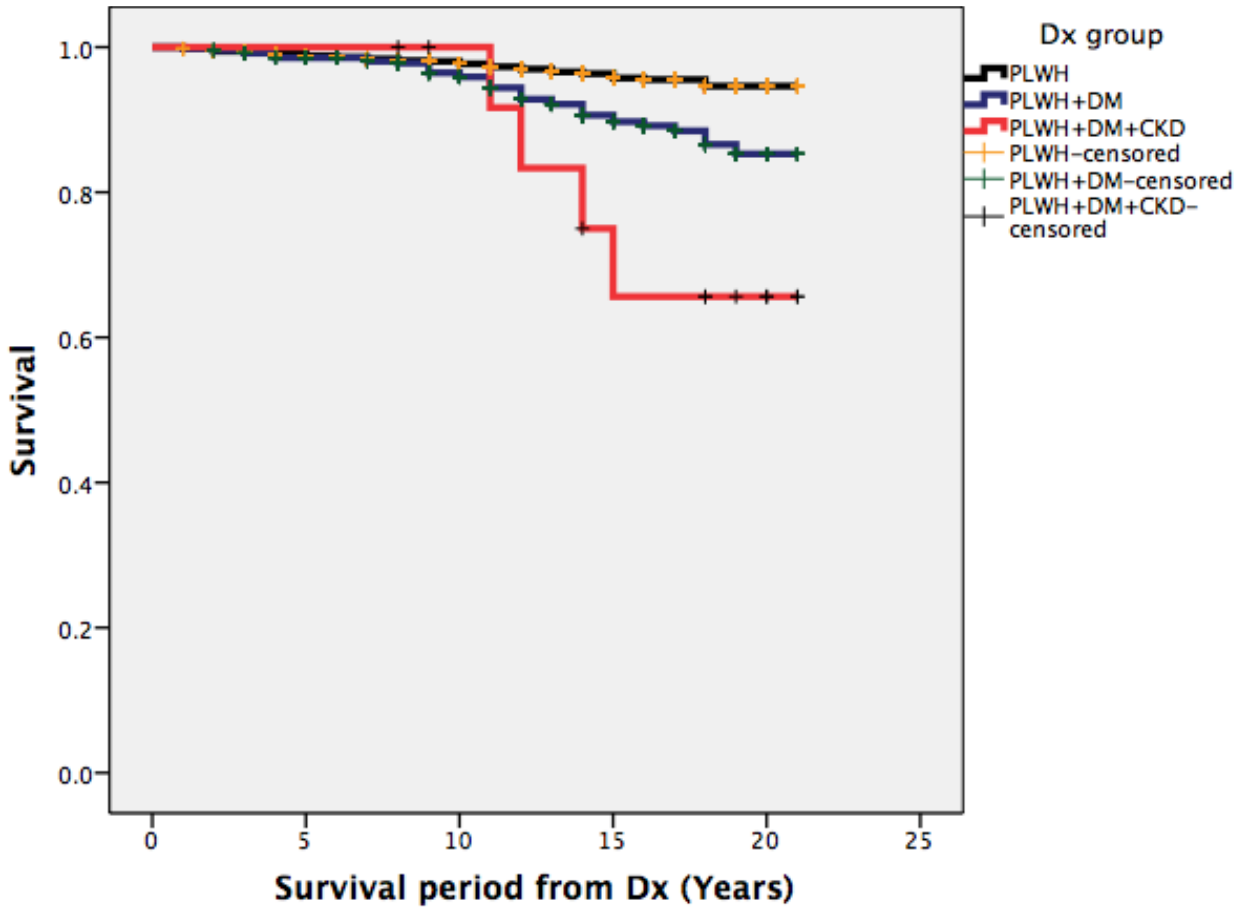

Figure 8. Kaplan-Meier survival curves for all-cause mortality among patients classified as ≤ 30 years old at initial clinic visit, log rank $p < 0.01$

Notes. censored; persons still survive at that point of the study, Dx; diagnosis

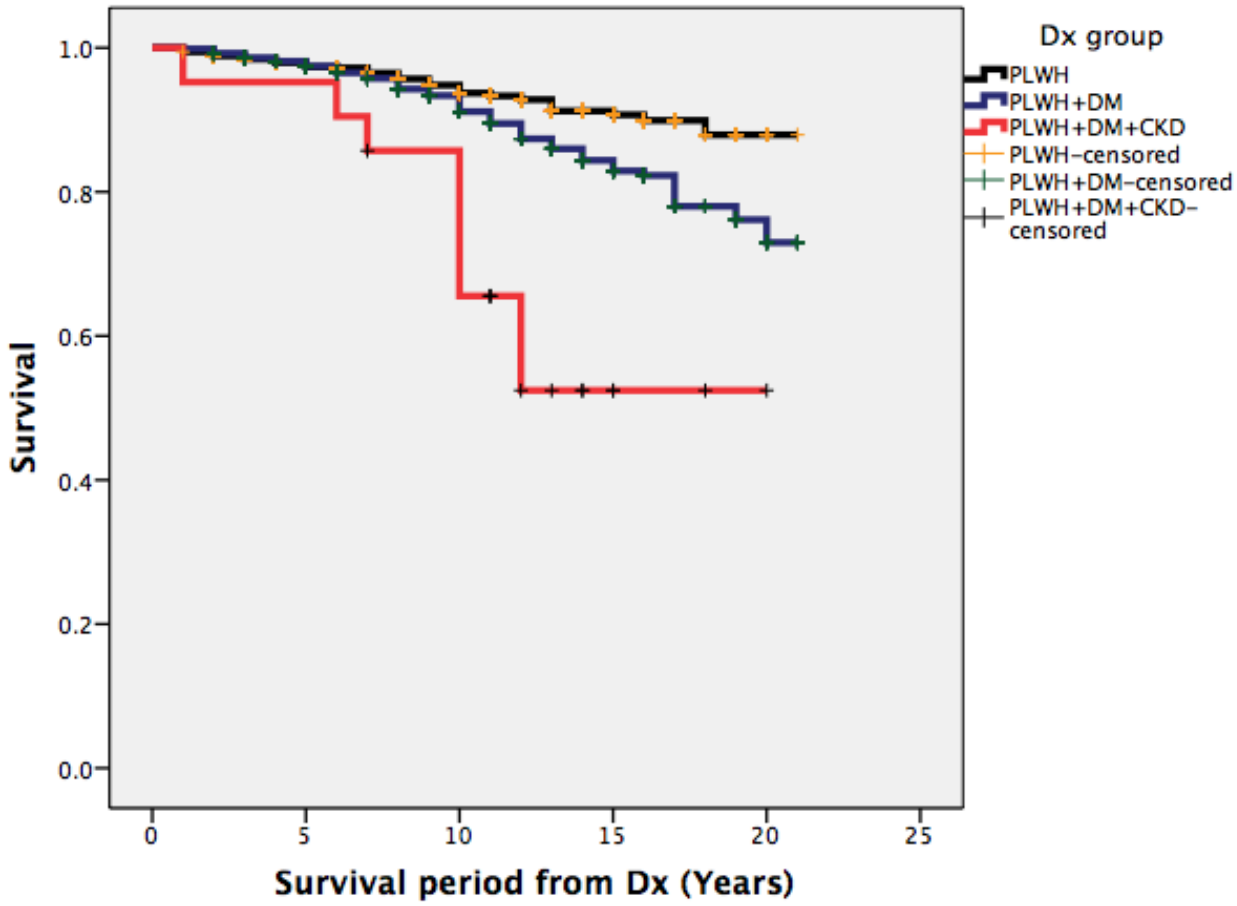

Figure 9. Kaplan-Meier survival curves for all-cause mortality among patients classified as 31-50 years old at initial clinic visit, log rank $p < 0.01$

Notes. censored; persons still survive at that point of the study, Dx; diagnosis

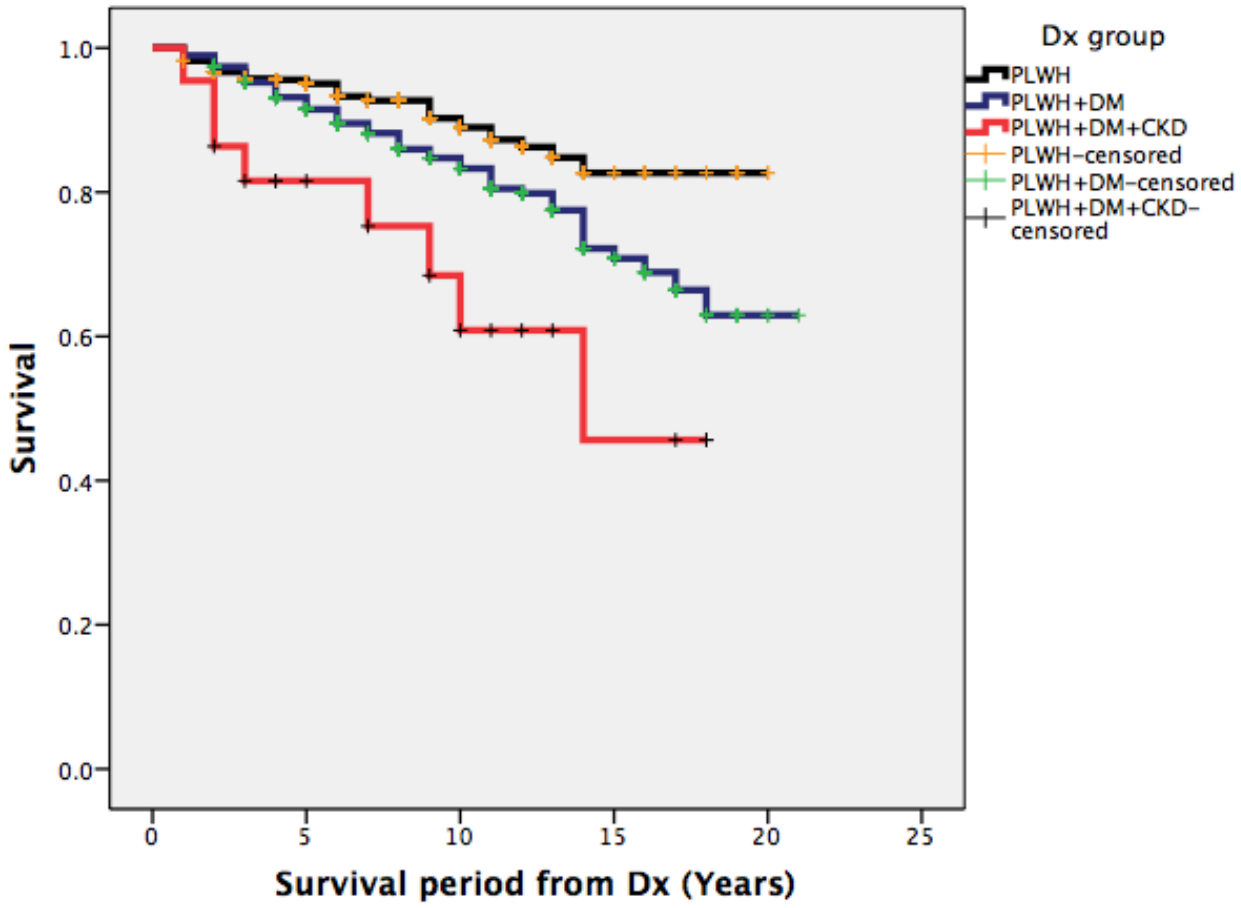

Figure 10. Kaplan-Meier survival curves for all-cause mortality among patients classified as over 50 years old at initial clinic visit, log rank $p < 0.01$

Notes. censored; persons still survive at that point of the study, Dx; diagnosis

Table 18. Risk factors in mortality rates

Criteria	Risk factors	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
								Lower	Upper
Age at initial clinic visit	≤ 30 years old			142.283	2	0.000			
	31-50 years old	0.79	0.113	49.11	1	0.000	2.203	1.766	2.747
	> 50 years old	1.453	0.122	142.097	1	0.000	4.275	3.366	5.428
Dx categories	PLWH-only			64.946	2	0.000			
	PLWH+DM	0.58	0.1	34.009	1	0.000	1.787	1.47	2.172
	PLWH+DM+CKD	1.556	0.231	45.557	1	0.000	4.739	3.016	7.446

Note. Dx: diagnosis

DISCUSSION

DM and CKD in PLWH negatively impact survival rates. There were no people who do not have CKD without DM in PLWH in this study. These results were to be expected. Because, as previous study indicated that DM is a risk factor for CKD in PLWH (Estrella & Fine, 2010). Comorbid conditions in PLWH increased with age, having DM occurs more frequently in African Americans, and the mortality rate increases with age (CDC, 2015). The survival time indicated that there was a significant difference between the three groups (PLWH, PLWH+DM, PLWH+DM+CKD) at significance level of $p < 0.01$. PLWH-only lived almost five years longer than PLWH+DM+CKD, no matter when diagnosed, and almost 1.5 years longer than PLWH+DM. The expected survival times were each reduced by the comorbid conditions, which concurs with Walensky et al. (2006) study.

In addition, having two comorbid conditions (PLWH+DM+CKD) resulted in higher mortality rates and decreased expected length of survival than having only one comorbid condition (PLWH+DM). The study's initial database did not capture the other possible influential factors such as body mass index (BMI), weight, height, or blood pressure that might affect the DM and CKD occurrences in PLWH. Thus, future research needs to capture possible variables to more accurately predict survival rates in three disease groups.

Moreover, our finding has shown that early age at initial clinic visit has positive effects with a longer survival time in every disease group. It could be related to the early retention in care in HIV patients. If PLWH have early age at initial clinic visit, they may possibly receive retention in care early, which in turn could affect life expectancy. Early retention in care is a major important success to manage HIV (Geng et al., 2010) because early retention in care positively affects viral load suppression and controls CD4 cell count, which protects against the development of AIDS (Horstmann et al., 2010; Mugavero, Amico, et al., 2012; Mugavero et al., 2010). As a result, it could be possible that early age at initial clinic visit affects survival time in PLWH.

In addition, findings also indicate that having CKD causes an increase in mortality rates for PLWH. There were more than four times higher mortality rates in PLWH with multiple diseases than those with a single disease. CKD is a dysfunction of the kidneys, and most of people will go to the ESRD stage, which correlates highly with mortality rates (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004). Thus, it is important to prevent CKD in PLWH.

LIMITATIONS AND FUTURE RESEARCH

Although this study has a large sample size, some limitations exists. First, each group population is different, especially with PLWH+DM+CKD. PLWH+DM+CKD had a small portion population as compared to the other two groups (PLWH, PLWH+DM). Thus, this circumstance might have bias in our study. However, the mortality rate was highest in this group as compared to the other two groups. Therefore, despite this study having some bias, it remains important. In future studies, researchers will need a larger sample of PLWH+DM+CKD to be more accurate. In addition, this study is a secondary database analysis, so it might have missing data and/or incorrect data entered from the initial data. Also, we do not know the initial date of patients' HIV diagnosis date, so, it might be biased to predict the survival rates. But this study used age at initial clinic visit, which in turn related in early retention in care. This study will thus contribute to retention to the literature in care and survival rates in PLWH with comorbid conditions. As a result, there could be unintentional bias to our study. Despite this, if we have or do not have missing or incorrect data entered in the initial data set, we have enough population portions to complete an analysis in our study, which could make the study come across as generalizing. Finally, during our study period, 2006 through 2015, most data have a large censored data, so there might be bias on calculating on the survival rate on our study, but the SPSS captured the censored data on each disease group.

CONCLUSION

We conducted an analysis of survival rates in PLWH, PLWH+DM, and PLWH+DM+CKD divided by age at initial clinic visit from 2006 through 2015. After adjusting confounding variables, we found that having a younger age at initial clinic visit results in having longer survival

time, regardless of group. Moreover, having comorbid conditions in PLWH usually led to decreased survival time than only having HIV infections. Thus, our study indicated that age at initial clinic visit and having comorbid conditions in PLWH affects the mortality rates in PLWH. Based on our knowledge, there is no study to compare the survival rates among PLWH, PLWH+DM, and PLWH+DM+CKD, so this study will contribute considerably to future studies on PLWH comorbid conditions.

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Chapter Five: Discussions, Implications, and Conclusion

This chapter includes a study overview, conceptual model development and provides findings and discussions, implications and recommendations, and conclusion. Specifically, an overview of the purpose of the study, research questions, the methodology, a statistical analysis, and findings are presented. Finally, a discussion of the findings followed by research questions; a discussion of strengths and limitations; and recommendations for nursing practice, future research, nursing education, and health policy are presented.

Study Overview

Over one million people have become afflicted with an HIV infection in the United States (CDC, 2017b), and 60% of persons living with human immunodeficiency virus (HIV) (PLWH) have comorbid conditions (Goulet et al., 2007). Diabetes (DM) is the common comorbid condition in PLWH (Brown et al., 2005; Butt et al., 2009; Medapalli et al., 2012), and it is the main cause of chronic kidney disease (CKD (Estrella & Fine, 2010), which closely relates with increasing mortality rates (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004). As such, is the need has emerged to study PLWH with comorbid conditions. These studies are a secondary data analysis using the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) data, which include human immunodeficiency virus (HIV) infected people who are over 18 years old and have been receiving combined antiretroviral therapy (cART) for more than 6 months. The study was designed to serve two goals. The first study goal (Aim 1) was to investigate retention in care measurements, to compare paths regarding their retention in care and disease control (CD4 cell count, hemoglobin A1c [HbA1c] level), and to investigate relationships between HIV symptom burden and retention in care between PLWH+DM as divided by two different age groups. The second goal (Aim 2) is to compare the long-term health outcomes of HIV and/or DM disease control on kidney function PLWH and PLWH+DM in the years 2006 through 2015, as well as survival rates differences among PLWH, PLWH+DM, and PLWH living with DM and chronic kidney disease (PLWH+DM+CKD).

Chapter Three (Aim 1), "Retention in Care and symptom burden in Persons Living with HIV with Diabetes for Adults over 50" is a longitudinal retrospective cross-sectional study and short-term goal of HIV care for PLWH+DM. Six methods are used to measure retention in care—missed visit (count, dichotomous), visit adherence, 4-month visit constancy, 6-month gaps in care, and the HRSA HAB measure (U.S. Department of Health and Human Services, 2016). The researchers based this study on the Mugavero, Westfall, et al. (2012) study, which indicated a 'gold standard' of retention in care measurement without considering comorbid conditions in PLWH. Aim 1 endeavored to investigate the retention in care measurements in PLWH+DM. This study gives to us the knowledge of measurements of retention in care for PLWH+DM and the different models of retention in care (missed visits [count], visit attendance, visit adherence, 4-month visit constancy) and health outcomes (disease control [CD4 cell count, HbA1c level]) between two groups in PLWH+DM (older adults living with HIV with DM [OALWH+DM] who are over 50 years old) and younger adults living with HIV with DM [YALWH+DM] who are 50 years old and under). Additionally, this study also reveals the relationships between HIV symptom burden and retention in care (the Health and Resources Services Administration HIV/AIDS Bureau [HRSA HAB measure]) in PLWH+DM.

Chapter Four (Aim 2), titled "Comparing 10-year Survival Rates in Comorbid Conditions in HIV-infected People Treated with Combined Antiretroviral Therapy (2006–2015)," included the results of a study that investigated the occurrence of CKD in PLWH and PLWH+DM and examined the survival rates among the three disease groups (PLWH-only, PLWH+DM, PLWH+DM+CKD). This is a longitudinal comparison retrospective study. This study can serve as a guide for PLWH+DM to prevent CKD and increase the survival rates. There is a lack of current research on how the HIV/DM disease affects CKD occurrence in PLWH+DM. Moreover, based on this researcher's knowledge, no survival rates of PLWH+DM+CKD have been studied.

To be considered for inclusion in the study, all the samples were aged 18 years or older and had been receiving cART for at least 6 months. For Aim 1, samples also must have DM verified by a HbA1c level > 6.5 % or have DM medications, and researchers only considered

participants who had at least one primary HIV-care appointment at a CNICS clinic site during the 2015 calendar year. For Aim 2, samples having PLWH and/or having comorbid conditions (DM, CDK) must have made at least one primary HIV-care visit to CNICS clinic sites in the 2006–2015 calendar years.

Demographic measures included age, present gender, race/ethnicity, CD4 cell count, and HbA1c level. For Aim 1, retention in care measurements included missed visits, visit adherence, visit attendance, and visit consistency (4-month visit constancy, 6-month gap, HRSA HAB measure) during 2015, and outcome variables were measured by disease control (CD4 cell count, HbA1c level). For investigating symptom burden and retention in care, this study used the HIV Symptom Index, which included 20-items for symptom burden and the HRSA HAB measure to retention in care. For Aim 2, CKD occurrence was measured by different disease groups in 2006–2015. To measure survival rates, the researchers placed samples into different groups by disease (PLWH, PLWH+DM, PLWH+DM+CKD) and age at initial clinic visit in from 2006 through 2015.

To answer the research questions, descriptive statistics, Spearman's correlation coefficients, logistic regression, path analysis, survival analysis, and cox regression were performed for data analysis using SPSS version 23.0 for PC (IBM Corp, Released 2015), and AMOS version 23.0 for PC (Arbuckle, 2014). Before conducting the statistical analysis, data errors were checked, missing data were managed, and assumptions were checked.

Overall, for Aim1, a total of 798 samples are in the category of PLWH+DM in 2015; 564 were in the OA group, and 234 were in the YA group. Most of the retention in care measurements were significantly correlated ($p < 0.05$), but 4-month visit constancy was not. Through the logistic regression, there were few relationships in retention in care measurements and CD4 cell count in OALWH+DM and YALWH+DM ($p < 0.05$) emerged. Only missed visits (count) variable was related to CD4 cell count in OALWH+DM ($p < 0.05$). As to paths analysis, OALWH+DM retention in care measurements related with the CD4 cell count only ($p < 0.05$); however, YALWH+DM related significantly with HbA1c level and CD4 cell count at a level of $p < 0.05$.

For symptom burden, no relationships existed between symptom burden and retention in care in YALWH+DM, but some of the symptoms that burdened patients (fatigue, sadness, memory loss) had a significantly negative relationship with retention in care (HRSA HAB measure) in OALWH+DM ($p < 0.05$). For Aim 2, 8,266 samples were in the PLWH category; 1,720 were categorized as PLWH+DM; and 57 were categorized as PLWH+DM+CKD during 2006 through 2015. The findings indicate that CKD always occurs in conjunction with DM in PLWH (e.g., CKD does not occur in PLWH without DM); having more comorbid conditions decreased survival time; and samples' survival time appeared lower when their initial clinic visit took place later and their age was higher ($p < 0.01$). The specific findings are described in the Findings and Discussion section.

CONCEPTUAL MODEL DEVELOPMENT

This study tested two conceptual models as there were no previous studies regarding retention in care in PLWH+DM. Thus, the Aim 1 model was based on the Mugavero, Westfall, et al. (2012) study, which presented the 'gold standard' retention in care measurements for PLWH without considering comorbid conditions. Mugavero, Westfall, et al. (2012) study suggested measurements including missed visits (count, dichotomous), visit adherence (continuous), 4-month visit constancy, 6-month gap, and the HRSA HAB measure. The study used the same model in PLWH+DM because the Mugavero, Westfall, et al. (2012) study had already tested the correlations between retention in care measurements. However, for our PLWH+DM group, the 4-month visit constancy showed no correlation between retention in care measurements ($p < 0.05$). Also, the Mugavero, Westfall, et al. (2012) study used health outcomes in the viral load, but this study used CD4 cell count and HbA1c level based on the disease differences. Furthermore, this study demonstrated the path analysis, which is not currently in research. This study demonstrated the different relationships between retention in care and health outcomes by different age groups in PLWH+DM. For Aim 2, the literature review served as basis for a conceptual model. PLWH+DM had more chances to have CKD according to previous studies (Estrella & Fine, 2010).

Thus, this study built the conceptual model for CKD occurrences in different disease groups (PLHW, PLWH+DM) and figured out the survival rates for the different disease groups (PLWH-only, PLWH+DM, PLWH+DM+CKD). The finding recognized that DM is a major risk factor for CKD in PLWH, and survival rates were affected by comorbid conditions and aging ($p < 0.01$). These findings are significantly important because there were no studies related by survival rates on different disease groups in PLWH, especially on DM or CKD. But to expand on this research, future studies need larger samples and more particularized research regarding comorbid conditions in PLWH.

FINDINGS AND DISCUSSION

This section describes study characteristics according to the research questions and divided by the aims. It includes study sample characteristics, retention in care measurements, CKD occurrences, and survival rates for different groups.

Findings Regarding Research Questions

Aim 1

Aim: Describe the population of OALWH+DM who visited the CNICS clinics during 2015.

Research question 1: What are the differences in demographic descriptive characteristics (age, gender, race/ethnicity) and baseline disease control (CD4 cell count, HbA1c level) between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

Research question 2: What are the differences in retention in care descriptive characteristics (missed visits, visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure) between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

- **Age.** OALWH+DM mean age was 59.35 years±7.22, and the mean age of the YALWH+DM was 44.56 years ±5.10.

- **Gender.** Both groups have more male participants than female (OALWH+DM: 80%, YALWH+DM: 71.4%) ($p = 0.01$). Of OALWH+DM, 20% were female and of YALWH+DM, 28.6% were female ($p = 0.01$).
- **Race/Ethnicity.** Of OALWH+DM, 45.2% were White-Non-Hispanic, but 31.2% was White-Non-Hispanic in YALWH+DM ($p = 0.001$). The most common race/ethnicity in YALWH+DM was African American-Non-Hispanic (45.3%), but only count 38.2% of OALWH+DM ($p = 0.001$).
- **HbA1c level:** More than half of the participants in both groups indicated that they have a HbA1c level higher than 6.5% (OALWH+DM: 64%, YALWH+DM: 65%). Still, no significantly difference in HbA1c level in either group occurred.
- **CD4 cell count:** OALWH+DM uncontrolled CD4 cell count levels (CD4 cell count of less than 499 cells/μL) were 32.5%, and YALWH+DM was 30.2%. Nonetheless, no significant difference existed between the two groups.
- **Missed visits.** YALWH+DM had a missed visits range was 0-12, and OALWH+DM was 0-5. Both groups had a mean number of visits at around three times during one year, which meets the Panel on Clinical Practices for Treatment of HIV Infection (2017) recommendation for HIV care. Despite this, no significant differences appear between the two groups.
- **Visit adherence.** Only 6% of participants in either group had less than 50% visit adherence, which was correlated with visit attendance rates. Thus, most PLWH+DM had good visit adherence during the 2015 calendar year.
- **4-month visit constancy, 6-month gap, HRSA HAB measure.** YALWH+DM had better 4-month visit constancy was 31% and OALWH+DM was 28.2%. 39.2% of YALWH+DM had 6-month gaps (not retained), and 6.8% of OALWH+DM had 6-month gaps (not retained). In the HRSA HAB measure, 33.7% of YALWH+DM had not retained and 29.9% of OALWH+DM had not retained. However, there is

no significantly differences among 4-month visit constancy, 6-month gap, and the HRSA HAB measure between two groups.

- In sum, the significantly differences in both groups at $p < 0.05$ level was gender, race/ethnicity, visit attendance. The other variables were not significantly different in both groups.

Research question 3: What are the correlations between retention in care measurements (missed visits [count, dichotomous]), visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure), and each other between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

Research question 4: What are the relationships between retention in care measurements (missed visits [count, dichotomous]), visit adherence, 4-month visit constancy, 6-month gap, HRSA HAB measure) and CD4 cell count between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

In this study, the below variables were significantly correlated in YALWH+DM.

- Missed visits (count), missed visits (dichotomous) and visit adherence variables were highly negatively correlated to one another (–0.852, –0.853, respectively, $p < 0.01$).
- Missed visits (count) and missed visits (dichotomous) were highly positively correlated (0.994, $p < 0.01$). This result was expected because missed visits (count) and missed visits (dichotomous) were the same variable, just presented differently.

In this study, the below variables had no significant or low significant correlations in YALWH+DM.

- 4-month visit constancy and 6-month gap had no significant correlation between missed visits (count, dichotomous) and visit adherence at a significance level of $p < 0.05$. Only 4-month visit constancy and the HRSA HAB measure had a low positive correlation (0.182, $p < 0.01$).

In this study, the below variables had significant high correlations in OALWH+DM.

- As with the YALWH+DM group, the missed visits (count) and missed visits (dichotomous) variables were highly positively correlated with each other (0.997, $p < 0.01$), and visit adherence and missed visits measurements were highly negatively correlated with missed visits (count; –0.854, dichotomous; –0.855) at a significance level of $p < 0.01$.

In this study, the below variables had no significant or low significant correlations in OALWH+DM.

- However, OALWH+DM had different results on the HRSA HAB measure. The HRSA HAB measure had no significant correlation with 4-month visit constancy, which is the opposite result from the YALWH+DM group.
- Both of 4-month visit constancy, 6-month visit gap had not significantly correlated with missed visits (count, dichotomous) variables.
- Missed visits (count, dichotomous), visit adherence, 6-month gap, and HRSA HAB measure had low correlations in OALWH+DM (0.130 to 0.179, $p < 0.01$).

In this study, the below section describes the association between retention in care measurements and CD4 cell count.

- There are no significant relationships in YALWH+DM between retention in care measurements and CD4 cell count. Except missed visits (count), there is also no significant relationships between retention in care measurements and CD4 cell count in OALWH+DM (Exp (B) = 11.277, confidence intervals [CI]: 1.499-84.843, $p < 0.05$).
- For this research question's majority of findings, there was no significant relationships between retention in care and CD4 cell count in OALWH+DM and

YALWH+DM at the significant level of $p < 0.05$. This research question need more future study because the previous study (Mugavero, Westfall, et al., 2012), which did not consider that the comorbid conditions in PLWH showed that viral load (VL) and retention in care had a significant relationships with each other.

- Overall, these correlations for both PLWH+DM age groups do not match with the findings of Mugavero, Westfall, et al. (2012). In the Mugavero, Westfall, et al. (2012) study, which suggested a gold standard retention in care measurements in PLWH, all the retention in care measurements were highly correlated with one another. However, this study which considered comorbid conditions in PLWH, not all retention in care measurements were significantly correlated with the other retention in care measurements in either different PLWH+DM age groups. Thus, we need to redefine retention in care measurements for PLWH+DM.

Research question 5: What are the differences paths in retention in care regarding HIV disease control (CD4 cell count) and DM disease control (HbA1c level) between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

The following sections describe the path relationships between independent variables (missed visits [count], visit attendance, visit adherence, 4-month visit constancy), and disease control (CD4 cell count, HbA1c level).

- **OALWH+DM**. The three hypothesized paths related significantly with CD4 cell count ($p < 0.05$): missed visits (count); visit adherence; and 4-month visit constancy. Missed visits (count) had a negative relationship with CD4 cell count (–0.46), as did visit adherence (–0.43), while 4-month visit constancy had a positive effect on CD4 cell count (0.22) within significance level of $p < 0.05$. But visit attendance did not significantly relate with CD4 cell count ($p < 0.05$). Still, all the paths demonstrated that there were no relationships between retention in care measurements and HbA1c level in OALWH+DM. These findings could be the

result of the fact that it is simply true that retention in care is not related to HbA1c level in OALWH+DM. Nevertheless, the results demonstrated that retention in care is a key component in predicting CD4 cell count in PLWH, which is in agreement with previous studies (Berg et al., 2005; Hogg et al., 1998; Lima et al., 2009; Mugavero, Amico, et al., 2012; Mugavero, Lin, Allison, et al., 2009; Tripathi et al., 2011; Walensky et al., 2006).

- **YALWH+DM.** Four hypothesized paths related significantly with either CD4 cell count or HbA1c level ($p < 0.05$). Missed visits (count) and visit adherence had significant negative relationships with CD4 cell count ($p < 0.05$). Contrary to the OALWH+DM group, missed visit (count), visit attendance and visit adherence had significant positive relationships with HbA1c level at the significance level of $p < 0.01$ (0.72, 0.32, 0.35, respectively). Despite this, 4-month visit constancy did not relationship with CD4 cell count or HbA1c level in YALWH+DM. These results demonstrate that, compared to the OALWH+DM group, YALWH+DM retention in care has relationships with both HIV and DM disease control, which concurs with the Geng et al. (2010) study. These findings are important because, through these results, we can see that CD4 cell count was significantly related to retention in care regardless of age in PLWH+DM, and if YALWH+DM had good retention in care, they could control both diseases.

Research question 6: What are the relationships between symptom burden (HIV Symptom Index) and retention in care (HRSA HAB measure) between OALWH+DM (> 50 years old) and YALWH+DM (≤ 50 years old)?

The following sections describe the relationships between independent variables (20-items in HIV Symptom Index—fatigue, fever, dizzy, neuropathy, forgetful, nausea, diarrhea, sad, anxious, sleep problems, skin problems, coughing, headache, loss appetite, bloating, muscle aches, sex problems, body fat, weight loss, and hair loss) with five response choices—0: I do not have

the symptom; 1: I have the symptom, but it does not bother me; 2: I have the symptom, but it bothers me little; 3: I have the symptom, and it bothers me some; or 4: I have the symptom, and it bothers me a lot (Justice et al., 2001) and retention in care (HRSA HAB measure—binary variable; 0: not retained; 1: retained 90-days gap).

- Three symptom burden (fatigue, memory loss, sadness) were significantly negatively ($p < 0.05$) related to retention in care in OALWH+DM (N = 348). Having less fatigue was 0.584 times more likely to be retained (CI: 0.363-0.938), decreased memory loss was 0.35 times higher retained (CI: 0.399-1.011), and less sadness was more than 1.937 times retained in OALWH+DM (CI: 1.235-3.038). Compared to the OALWH+DM, there is no significant association between symptom burden and retention in care in YALWH+DM ($p < 0.05$). The study findings demonstrated that fatigue, sadness, and memory loss burdens might affect the retention in care in OALWH+DM more than YALWH+DM. These findings are important for the future because, having symptom burden effect to the older population retention in care in PLWH.

Aim 2

Aim: Investigate the effect of comorbid conditions of DM and CKD on the survival rates of PLWH+CKD who visited the CNICS clinics from 2006 through 2015.

Research question 1: What are the different characteristics (age, gender, race/ethnicity, mortality, CD4 cell count, HbA1c level) among PLWH, PLWH+DM, and PLWH+DM+CKD during the years 2006—2015?

Research question 2: What is the occurrence of chronic kidney disease (CKD) among PLWH and PLWH+DM who visited the CNICS clinics in the years 2006—2015?

The following section describes the different study characteristics and CKD occurrence by different groups.

- **PLWH-only.** The total number of samples in PLWH-only was 8,266 in the years 2006 through 2015. Most of them were no more than 50 years old (69.8%), male (84.7%), and White (51.3%). As a baseline of CD4 cell count, 36.7% had no more than 500 cells/μL (n = 946), 3.6% died during the 2006—2015 time frame, and the age group with age at initial clinic visit was patients in their 30s (34.6%).
- **PLWH+DM.** A total of 1,720 participants had PLWH+DM in 2006 through 2015. Most of these PLWH+DM were over 50 years old (74.9%), male (74.7%), and African American (48.9%). This group most commonly made an initial clinic visit in their 40s (38.3%). The proportion with a baseline CD4 cell count of no more than 500 cells/ μL was 42.2%, and 54.5% had a HbA1c level over 6.5% (n = 288). Of the total 1,720 PLWH+DM, 12% died during the 2006—2015 time frame.
- **PLWH+DM+CKD.** The samples included 57 participants. Most of them were over 50 years old (68.4%), male (68.4%), and African American (73.7%). PLWH+DM+CKD most commonly went to their initial clinic visits in their 40s and 50s (36.8%, 28.1%, respectively). Of the 57 PLWH+DM+CKD, 36.8% died in the 2006—2015 time frame.
- Overall, the total number of samples who enrolled in the CNICS during 2006 through 2015 was 10,063. Among them, 1,720 PLWH had DM, and 57 people had DM with CKD. DM is one of the major risk factors of CKD in PLWH (Estrella & Fine, 2010). Furthermore, no PLWH had only CKD without DM. In addition, we also found that as age increases, more comorbid conditions (DM, CKD) occur in PLWH. These results had been predicted because incidence of chronic illness diseases such as DM and CKD increased with age (Mpondo, 2016; Negin et al., 2012; Vigouroux et al., 1999; Webel et al., 2015). Among the three disease groups, the highest mortality rate was in PLWH+DM+CKD. This was expected because having CKD is highly correlated with a higher mortality rate (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004).

Research question 3: What is the 10-year survival rates among PLWH, PLWH+DM, and PLWH+DM+CKD who visited the CNICS clinics (2006—2015)?

The following section describes the different 10-year survival rates for different disease groups in 2006–2015.

- Of 10,030 people, 494 died from 2006 to 2015, and the total mean of survival time was 19.689 years (CI: 19.572-19.806). In PLWH-only, 5,265 people went to their initial clinic visits at no more than 30 years old, and the highest mortality rate group was those no more than 30 years of age at initial CNICS clinic visit. But PLWH who had comorbid conditions (DM, CKD) completed an initial clinic visit at age 30, and the highest mortality rate group went to an initial clinic visit age at more than 30 years old. These results indicated that having chronic diseases occurred more frequently in samples of higher ages, and having more comorbid conditions in PLWH led to decreased survival time than without comorbid conditions in PLWH, which remains consistent with the Braithwaite et al. (2005) study. One reason could be that having comorbid conditions are possible for PLWH to have a symptom burden (Gay et al., 2011; Gonzalez et al., 2007) because symptom burden creates a negative correlation with disease control in PLWH (Gay et al., 2011; Gonzalez et al., 2007). The mean survival time in PLWH was only 20.135 years (CI: 20.025-20.246); 18.691 years (CI: 18.404-18.979) in PLWH+DM; and 15.433 years (CI: 13.572-17.294) in PLWH+DM+CKD ($p < 0.01$).
- Patients' survival time means decreased when the age at initial clinic visit was older in all groups. If people were younger at initial clinic visit when they were no more than 30, their life expectancy would be around 20.451 years (CI: 20.341-20.56); however, if the age at initial clinic visit came after 50 years old, life expectancy was reduced by 2.516 years in PLWH-only ($p < 0.01$). With age at initial clinic visit at 30 years old and under, PLWH+DM life expectancy is around 19.768 years (CI: 19.404-20.132), but with age at initial clinic visits over 50, the life expectancy falls

to 17.129 years (CI: 16.386-17.872) ($p < 0.01$). For PLWH+DM+CKD, 18.271 (CI: 16.046-20.496) years was the life expectancy for those whose visit age at initial clinic visit were no more than 30, but after turning 50, the survival time was significantly reduced, to 12.53 years (CI: 9.639-15.421) ($p < 0.01$). In addition, when we controlled covariate factors (race/ethnicity, present sex, age groups, baseline CD4 cell count, initial HbA1c level, age at initial clinic visit, disease groups) that could influence the survival time of each group, only the age at initial clinic visit affected survival time ($p < 0.05$). The results demonstrated that PLWH+DM has a higher mortality rate than PLWH-only (CI: 3.366-5.428, $p < 0.01$) by 4.275 years, and the PLWH+DM+CKD mortality rate was 4.739 years higher than PLWH-only (CI: 3.016-7.446, $p < 0.01$). The reason for having lower survival rates in PLWH+DM+CKD than the other two groups (PLWH, PLWH+DM) is because mortality rates relate closely to kidney disease (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004). Forty-five percent of CKD cases will develop into end-stage renal disease (ESRD) (Gilmore, 2006; Whaley-Connell et al., 2009). The five-year survival rate is 35% in the general population (Collins et al., 2014), and 33% in PLWH (Soleymanian et al., 2006), and one of the risk factors of ESRD is an AIDS-defining illness (Abraham et al., 2014). As a result, it could be possible to decrease survival rates for patients having CKD than without CKD in PLWH.

STRENGTHS AND LIMITATIONS

The study has limitations. First, the study used a secondary data analysis retrospective longitudinal chart review from the CNICS, which might limit the generalizability of its findings because only the CNICS samples have been included in the studies. Second, there was missing data for disease control data (CD4 cell count and HbA1c level), so the results could be biased. Third, the CNICS data could possibly be incorrect, so the analysis could be biased based on results.

Last, the studies conducted a medical chart review from the CNICS data files, so they were limited by the variables included by the CNICS. Taking this into account, uncontrolled confounding factors might exist. Despite these notable limitations, the CNICS has eight clinic sites and more than 32,000 HIV-infected people who have been receiving cART for more than six months. Our findings can therefore serve as a guide to healthcare providers and PLWH.

Even though the study had limitations, it bears important findings. The study focused on retention in care in PLWH+DM by different age groups, CKD occurrence, and survival rates in PLWH, PLWH+DM, and PLWH+DM+CKD.

The study also had several strengths. Aim 1 addressed the comparison of retention in care in PLWH+DM by two age groups, making this the first study regarding comorbid conditions in PLWH divided into OA and YA groups. The results were significantly important because, through them, we can determine the significant paths and measurements between retention in care in PLWH+DM by different age groups. Aim 2 addressed the CKD occurrence and survival rates in different disease groups. This study is the first study to compare survival rates categorized by diseases, and this study used data from a comparatively long study period of over 10 years, so the results may have more representative data regarding CKD occurrences and survival rates. These findings will provide a good research foundation regarding developing comorbid conditions in PLWH.

NURSING IMPLICATIONS AND RECOMMENDATIONS

Implications for Nursing Practice

Knowing that having comorbid conditions in PLWH results in poorer survival rates than PLWH-alone, nurses should focus on symptom control such as fatigue and neuropathy problems, which are common symptoms in both DM and HIV (American Diabetes Association, 2015; Wilson et al. 2016) to improve health outcomes. Still, this might not be enough for PLWH+DM because HbA1c level was not correlated with retention in care in OALWH+DM. Additional interventions to improve health outcomes thus become necessary, such as reducing barriers

including assessments, social support, and transportation. For example, nurses need to assess barriers of PLWH+DM the first time patients visit the clinics and introduce the connection to reduce the barriers. Moreover, nurses can assess patients' transportation needs and social support. If the patients have barriers to transportation and social support, nurses can make connections to social workers or public health nurses to resolve those problems and improve health outcomes.

Through the perspective of keeping retention in care, nurses need to assess cART side effect such as DM and CKD occurrence. Because DM is the main causes of CKD (Estrella & Fine, 2010) and it is important to take care about kidney functions in PLWH, kidney disease related to mortality and morbidity rates after patients started in cART (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004). Among PLWH, 17% developed CKD (Post & Holt, 2009), and among them 45% progressed to end stage renal disease (ESRD) (Gilmore, 2006; Whaley-Connell et al., 2009), which is highly associated with mortality and morbidity (Adedeji et al., 2015; Kim et al., 2011; Szczech et al., 2004). Thus, it remains important to keep monitoring kidney functions in PLWH. Additionally, nurses need to educate patients to keep going on to clinic (retention in care) for improving health outcomes because retention in care is a key management component in PLWH (Geng et al., 2010). Resultantly, when doctors diagnose patients with PLWH, nurses should educate patients that they keep going to clinics to prevent comorbid conditions, which are highly correlated with the mortality rates in PLWH.

Moreover, HIV and DM require patient self-management, and patients need care at the community level. This study's findings revealed that OALWH+DM with three symptom burden (fatigue, sadness, and memory loss) had poor health outcomes. Also, OALWH in the community are suffering from comorbid conditions such as DM, CKD, and depression. Despite this, a lack of support for PLWH with comorbid conditions in the community is apparent. One way to break down methods is to educate the public health nurses who are caring for PLWH closely in the community. Thus, in the future, we need to provide more education programs to public health nurses to improve health outcomes in PLWH at a community level.

Recommendations for Future Research

These are some recommendations for future research based on studies findings. Although researchers have consistently shown the negative impact of poor retention in care on HIV health outcomes (Horstmann et al., 2010; Mugavero, Amico, et al., 2012; Mugavero et al., 2010), the study (Aim1) is the first study to examine comorbid conditions (DM and/or CKD) in PLWH. The findings from this study provide ample guidance for measuring retention in care in PLWH who have comorbid conditions. Still, most of the retention in care measurements in PLWH+DM did not significantly affect on the HbA1c level in OALWH+DM. Because the HbA1c level and most of retention in care measurements had significant relationships in YALWH+DM, the HbA1c level may be more influenced by other variables such as symptom burden, and medications. Future studies need to clarify the influencing factors on HbA1c level in OALWH with comorbid conditions.

In determining the survival rates of different disease groups (Aim 2), the findings indicated that having CKD had the lowest survival time of the three disease groups. Also, age at initial clinic visit and aging had an affect on survival time. There could be more confounding factors, however, such as VL, medications, and length of time receiving cART, which can also affect survival rates. VL suppression indicated that HIV management can be conducted well by taking different medications (e.g., tenofovir) that have different side effects, so it could be brings to PLWH comorbid conditions such as DM, and the duration of receiving cART will have a positive effect on survival times in PLWH. To expand our knowledge of survival time for different diseases, more research need to be undertaken that controls possible confounding factors and includes larger samples.

Recommendations for Nursing Education

Even though a large portion of people are suffering by the HIV/AIDS infection in the U.S. (CDC, 2017b), there are no specific classes for the HIV/AIDS in the bachelor degree course work. The essentials of a baccalaureate education for professional nursing practice (American

Association of Colleges of Nursing, 2008) indicated that baccalaureate-educated nurses need to prepare to care for patients of all age groups, and we need to pay more attention to OA because this population has more chorionic illnesses and comorbid conditions such as mental disorders. However, comorbidities are not addressed specially in any nursing classes taken at the bachelor degree level (American Association of Colleges of Nursing, 2008). Nurses need to recognize that comorbid conditions have more complex disease symptoms, and then they need to consider the side effects of any necessary medications. Comorbid conditions should therefore be added to the curriculum based on the increase in comorbid conditions not just in patients with HIV but in the aging population.

Recommendations for Health Policy

The vision of the National HIV/AIDS strategy released by the White House in 2015 was to reduce gaps in HIV care (White House Office of National AIDS Policy, 2015). One of its goals was to "increase access to care and improve health outcomes among PLWH" (White House Office of National AIDS Policy, 2015, p.9). Thus, followed by the White House Office of National AIDS Policy (2015), suggested the stage care system, which we called 'the HIV care continuum' or 'HIV treatment cascade', which involves a focus on total care of HIV-infection from diagnosis through achieved VL suppression. To provide appropriate care for PLWH, we need to initiate the cascade of care that includes optimum care for PLWH: identification of infection; linkage to initial HIV treatments; retention in care; and treatment adherence (Gardner et al., 2011). But the most important point of the HIV treatment cascade is retention in care. The high mortality rates can be explained in part by poor retention in care (Mugavero, Amico, et al., 2012). According to the CDC data, only 40% of PLWH stay in care, and 70% of PLWH in the United States in 2011 did not have their HIV-infection under control (Bradley et al., 2014). This reason could be followed by many other reasons, but one possible obstacle could be having comorbid conditions in PLWH because following the development of cART, OALWH had more of a chance to live longer and

thereby to develop chronic diseases (Negin et al., 2012) and our findings indicated that having more comorbid conditions affected the retention in care in OALWH.

The Braithwaite et al. (2005) study indicated that non-HIV-induced mortality rates are increasing in PLWH due to them having a chronic disease, which corresponds with findings of survival rates: having more comorbid conditions such as DM and CKD results in having poor survival rates in PLWH. The researcher recommend that HIV clinics should develop a nursing policy of early detection of comorbid conditions in PLWH such as screening for DM and CKD. At some point, patients should undergo screening for HIV infections in underserved populations, whether they have insurance or not, to provide for the early detection of HIV and prevent transmission of HIV. From this point of view, the studies' findings raise awareness of comprehensive retention in care and the effects of survival rates in different comorbid conditions.

CONCLUSION

This chapter discussed overall study findings from Chapter 3 and Chapter 4 that were related to the study purpose. PLWH is one of the top priorities for care needs in the United States. As development of HIV treatments (cART) and comorbid conditions in PLWH are steeply growing (Effros et al., 2008), one of the most common dual diagnoses is DM and CKD (Brown et al., 2005; Butt et al., 2009; Medapalli et al., 2012; Naicker et al., 2015). DM, CKD, and HIV are chronic conditions that are important to manage. Having a chronic disease affects a person's symptom burden, and it causes poor health outcomes (Gay et al., 2011; Gonzalez et al., 2007). Thus, it is important to take care of comorbid conditions in PLWH. This study has two main aims: 1) investigate retention in care measurement in PLWH and in OWLWH+DM and YALWH+DM and recognize the association between symptom burden and retention in care in OWLWH+DM and YALWH+DM; and 2) comparing CKD occurrence and survival rates in PLWH, PLWH+DM, and PLWH+DM+CKD. The studies demonstrate retention in care and health outcomes according to age group in PLWH+DM, recognize that symptom burden (fatigue, sadness, memory loss) can affect the retention in care in OALWH+DM, and investigate the CKD occurrence and survival

rates in different disease groups. The results of the studies will contribute to nursing practice, research, and policy to address the comorbid conditions in PLWH, especially with DM and CKD in PLWH.

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Vita

Jungmin Park was born in South Korea to a family that consisted of several nurses. It was natural for her to go to nursing school when she graduated from high school. After graduating from nursing school, she worked as a registered nurse in an intensive care unit in South Korea. During her hospital clinic experience, she realized that many patients had preventable health conditions but who opted not to go to the hospital until they had more serious conditions. This generated a newfound interest in her that made her want to pursue both a master's degree in health education and management at the Ewha Womans Unviersity and a Ph.D. in nursing at the University of Texas at Austin, School of Nursing. During her master's degree program, she studied health education in disparate populations, especially focusing on occupational health. Her current research interest includes disease self-management by people in the HIV-infected population who have comorbid conditions, especially focusing on patients with diabetes and chronic kidney disease.

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